A Dissertation on

LIVER ENZYMES AS AN EARLY PREDICTOR OF COMPLICATED DENGUE FEVER

Dissertation Submitted to

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With partial fulfillment of the regulations for the award of the degree of

M.D. PAEDIATRICS

COIMBATORE MEDICAL COLLEGE, COIMBATORE

MAY 2019

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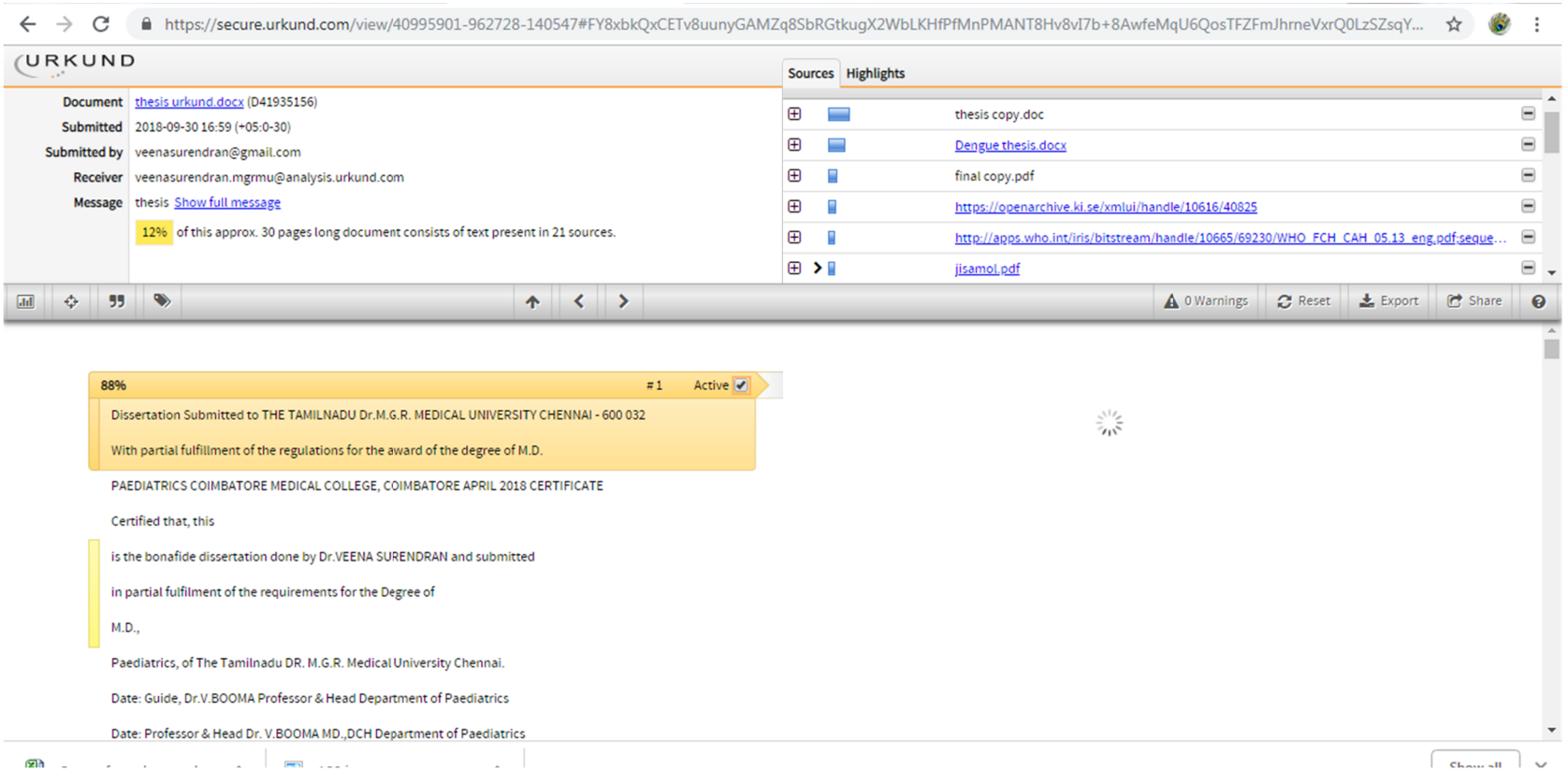
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This is to certify that this dissertation work titled "**LIVER ENZYMES AS AN EARLY PREDICTOR OF COMPLICATED DENGUE FEVER**" of the candidate **Dr. VEENA SURENDRAN** with registration number **201517303** for the award of **M.D Paediatrics,** is personally verified by me from the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **12 %** of plagiarism in the dissertation.

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DECLARATION

I solemnly declare that this dissertation titled **"LIVER ENZYMES AS AN EARLY PREDICTOR OF COMPLICATED DENGUE FEVER"** was done by me in the Department of Paediatrics, Coimbatore Medical College, during the period from JULY 2016 to JULY 2017 under the guidance and supervision of **Prof. Dr. V. BOOMA, M.D.** This dissertation is submitted to **The Tamilnadu Dr. M.G.R. Medical University** towards the partial fulfillment of the requirement for the award of MD Degree in Paediatrics.

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LIST OF ABBREVATIONS

ADE	-	Antibody Dependent Enhancement
ALT	-	Alanine Transaminase
AST	-	Aspartate Transaminase
CF	-	Cytotoxic Factor
DB	-	Direct Bilirubin
DF	-	Dengue Fever
DHF	-	Dengue Haemorrhagic Fever
DSS	-	Dengue Shock Syndrome
DV	-	Dengue Virus
HLA	-	Human Leucocyte Antigen
IFN	-	Interferon
iNK	-	Invariant Natural Killer
IL	-	Interleukin
INR	-	International Normalized Ratio
IgM	-	Immunoglobulin M
NS1 Ag	-	Non Structural protein 1Antigen
GB	-	Gall Bladder
RT-PCR	-	Reverse Transcriptase Polymerase Chain Reaction

SGOT	-	Serum Glutamate Oxaloacetate Transaminase
SGPT	-	Serum Glutamate Pyruvate Transaminase
TB	-	Total Bilirubin
TGF	-	Transforming Growth Factor
TNF	-	Tumor Necrosis Factor
USG	-	Ultra Sono Gram
WHO	-	World Health Organization

INTRODUCTION

Dengue is the most rapidly spreading mosquito –borne viral disease of mankind, with a 30-40 fold increase in global incidence over the last five decades. It is a major public health concern throughout the tropical and subtropical regions of the world. Almost half the world's population lives in countries where dengue is endemic.[1]

Dengue is the most rapidly spreading mosquito –borne viral disease of mankind, with a 30-40 fold increase in global incidence over the last five decades. It is a major public health concern throughout the tropical and subtropical regions of the world. Almost half the world's population lives in countries where dengue is endemic.[1]

The first description of dengue fever as "water poison" in relation to flying insects is given in one of the Chinese medical encyclopedia from the Jin Dynasty (265-420 AD)[3].The word "dengue" has its origin from Ka-dinga pepo, a Swahili phrase which means "cramp-like seizure caused by an evil spirit". The Swahili word "dinga" may possibly have its origin in the Spanish word "dengue" meaning fastidious or careful, which would describe the gait of a person suffering the bone pain of dengue fever. Slaves in the West Indies who contracted dengue were said to have the posture and gait of a Dandy, and the disease was known as "Dandy fever".

Clinical dengue epidemics were first reported more or less concurrently in Asia, North America, and Africa in the 1780s [3]. The earliest clinically reported case was from 1789 by Benjamin Rush in Philadelphia. He coined the term "break bone fever" as myalgia and arthralgia are the common symptoms. The term ‘dengue fever’ came only after 1828.[3]

The incidence of dengue is rising globally by about 30 fold in the past few decades. In the present decade its spread is shifting from urban to rural areas. About 100 countries are endemic; approximately 50 million degree infections occur annually and about 2.5 billion people are at risk in the tropical and subtropical areas. Therefore the WHO and its member states are giving greater commitment to dengue[28,29,30].

AIM

To evaluate if elevated liver enzymes can be used as an early predictor of severe dengue fever.

OBJECTIVES

PRIMARY OBJECTIVE:

Clinico epidemiological profile and outcome of Dengue in a tertiary care hospital

SECONDARY OBJECTIVES:

1. To prove the hypothesis that elevated liver enzymes can be used as an early predictor of severe Dengue fever.

2. To determine correlation between levels of Liver enzymes with Dengue severity.

STUDY JUSTIFICATION

Dengue fever is an important arboviral infection in tropical and subtropical areas. Severe dengue fever has got a significant mortality rate.

DF has an unpredictable clinical course which leads to a policy of indiscriminate referral to higher centres from peripheral centres. It is not very easy to assess which patient will progress from a non severe to severe case particularly in the early stages. Diagnosing dengue early is challenging because the initial symptoms of dengue infection are non specific and serological tests which are the mainstay of current lab diagnosis can confirm dengue only late in the course of the illness. Also, it is important to start the correct early management to have a better outcome.

Analyses of DF patients have showed that in addition to characteristic features of DF like –Fever, headache, arthralgia, myalgia, retro-orbital pain, vomiting, skin rash, thrombocytopenia and hemorrhagic manifestations- there are other features like hepatic dysfunction including an elevation in serum aminotransferase levels, hepatomegaly , ascites , pleural effusion and leucopenia[2]

Many laboratory investigations helps us in diagnosing, prognosticating and determining the outcome of the disease like CBC, LFT, NS1Ag, IgM Dengue, IgG Dengue etc.

There have been some studies conducted on the hepatic involvement in DF. Many studies found association between elevated liver enzymes and severity of dengue disease. But only a very few studies have been conducted in the paediatric population.

IgM Dengue test widely used for the confirmation of Dengue is reliable only during the second week of illness. Drop in platelets and rise in haematocrit which can be used to identify the onset of leaky phase, cannot be used as a prognostic marker. Hence there is a lacunae in diagnosing Severe Dengue fever early. Therefore this study was undertaken to address this issue and help clinicians to diagnose severe dengue fever early with liver enzyme levels and predict the prognosis of the disease according to the degree of elevation of liver enzymes.

REVIEW OF LITERATURE

GLOBAL SCENARIO

Although the full global burden of the disease is still uncertain , the patterns are alarming for both human health and economy. Every year ,it is estimated that 75 to 100 million cases of dengue infection and about 5, 00,000 cases of DHF occurs ,of which 20,000 lead to death. The loss of economy is 264 Disability –Adjusted Life Years (DALYs) per million population per year.[4]

Epidemics involving thousands of people and multiple virus serotypes recur in areas of Tropical Asia, Oceania, Africa and the America .

The global spread of both arthropod vectors and the viruses have led to the world wide resurgence of dengue epidemics including the emergence of DHF in the past 25 years. The world wide incidence of dengue has increased dramatically in recent decades. There is under reporting of dengue cases. About 390 million dengue infections per year have been estimated of which 96 million have clinical manifestations. Epidemics of severe dengue were experienced only in nine countries before 1970. But now it is endemic in more than 100 countries in WHO region of Africa America, Eastern Mediterranean, South East Asia and western Pacific. The number of reported cases is increasing recently. Not only the number of cases is increasing but also the case fatality rate is increasing.[5,6,7]

The outbreak of DF exists even in European countries and dengue spread was documented for the first time in France and Croatia in the year 2010 and imported dengue infections were reported in many other European countries. There was an outbreak of Dengue on the Madeira Islands of Portugal which led to over 2000 cases and imported cases were found in Mainland Portugal and many other European countries. In Florida and Yunnan province of China cases happened in 2013. Several South American countries like Costa Rica, Mexico and Honduras had out breaks of DF.

Coming to Asia, out breaks have been reported in Lao and Singapore. Number of cases goes on increasing in China, Fiji, Malaysia, the Cook Islands and Vanuatu especially with DEN 3. In 2015 several cases were reported from Brazil and Japan. Extensive number of cases is being reported from the Pacific Island Countries of Fiji, Tonga and French Polynesia. About 5, 00,000 people with severe dengue infections are hospitalized every year, especially children, these about 2.5% cases die.

WHO South East Asia (SEA) And Western Pacific regions

About 75% of dengue cases happen in Asia-Pacific. Dengue is one among the leading causes of hospitalization and death in children from these regions.

The rates of reported cases vary in each of the SEA countries, as they include suspected, probable or laboratory confirmed cases. The number of

cases in SEA goes on increasing over the last decade. The highest number of dengue cases in 2003 was reported from the 8 countries – India, Bangladesh, Indonesia Myanmar Maldives, Srilanka, Thailand and Timor Leste. The first dengue outbreak in Bhutan was reported in 2004. Nepal reported indigenous dengue cases for the first time in 2006 November. Indigenous cases were reported from all SEA countries except Korea by 2009. Cyclic epidemics are increasing in frequency. [8,9]

So the eight SEA countries are now classified as hyper endemic with all four of the serotypes of dengue virus. Severe dengue is endemic in most SEA countries. Overall reported case fatality rate for the region is about 1%; but in India, Indonesia and Myanmar the case fatality rates exceeds 3%.

The greatest burden of DF is currently found in Cambodia, Malaysia , Singapore, the Philippines and Vietnam. Maximum cases are reported from the four countries -Cambodia, Philippines, Malaysia andVietnam[10].

From the pacific region, 91% of reported cases came from French Polynesia ,Vanuatu, Australia and New Caledonia. Severe dengue infections are common in Island nations in the Pacific. Australia reported more than 1000 cases of DF in the year 2009 & 2010.

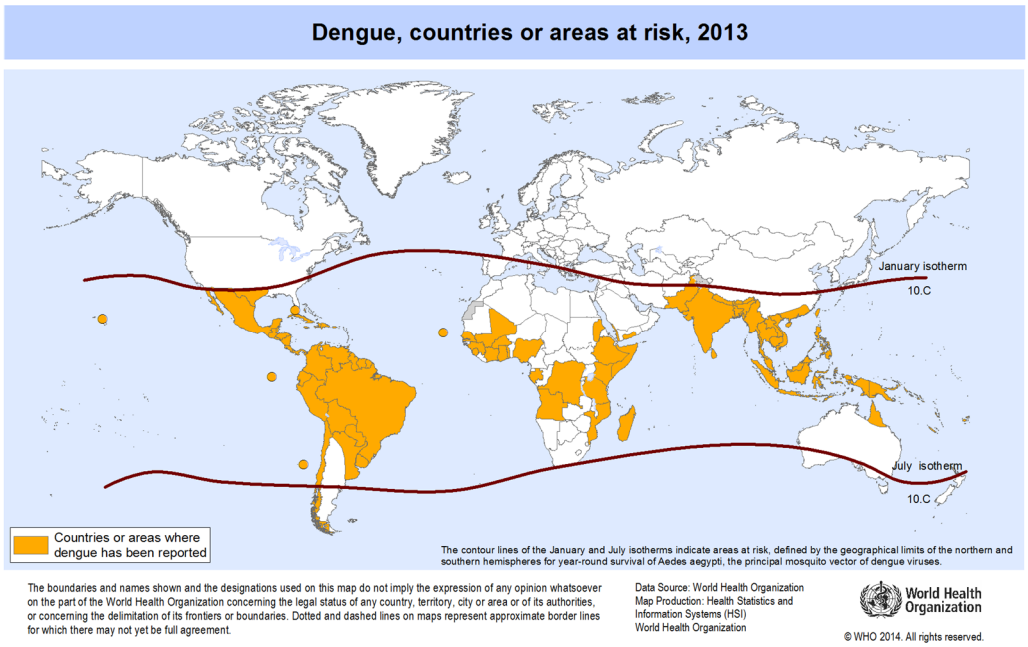


Figure 3.1: Reported cases of Dengue/DHF in various regions of the world

NATIONAL SCENARIO

In India Dengue is rapidly emerging and its prevalence is known for about 230 years. Dengue virus was isolated in India for the first time in 1945. The first evidence of occurrence of dengue fever in the country was reported in 1956 from Vellore district in Tamil Nadu. The first dengue hemorrhagic fever (DHF) outbreak occurred in Calcutta (West Bengal) in 1963.[11,12]

The incidence of DF is dramatically increasing in the recent years. India and the state Tamil Nadu are no exceptions. Many parts of India witness outbreaks of DF commonly during monsoon months and later, every year.

Dengue outbreaks are reported from Rajasthan, Jammu, Delhi, Calcutta, Gujarat and Maharashtra in 1970s and 1980s.Since 1988 DHF had its occurrence in many states of India.[11,12,14] The first main extensive DHF / DSS epidemics happened in our country in the year 1996 involving areas around Delhi and Lucknow[15] and later it spread to all the country[16].

The National Vector Born Disease Control Programme (NVBDCP) reports 28,292 cases and 110 deaths in the year 2010, which increased to 50,222 cases and 242 deaths during 2012. In 2013 75,808 cases and 193 deaths occurred. The case fatality ratio (CFR) in 1996, 2010 and 2014 are 3.3% , 0.4% and 0.3% respectively[17,18,19]. In 2014, 33320 cases and 86 deaths were reported. Thus reduction is probably due to the cumulative effects of better patient management, increased diagnostic capabilities and better reporting. The number of DSS cases in India remains low when compared with the rest of South – East Asia.

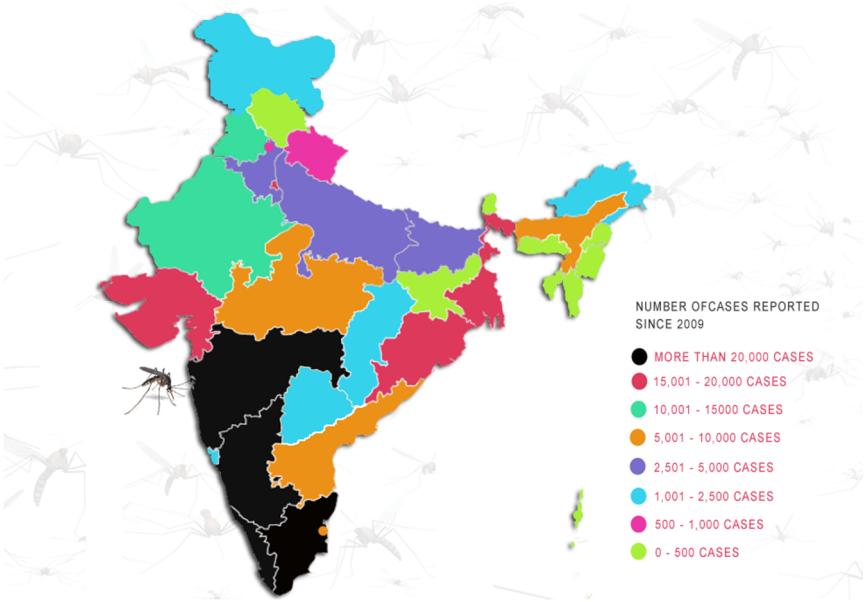


Figure 3.2: Dengue endemic areas in India

For the five years (2008–2012), NVBDCP reported about 22,584 dengue cases from Tamil Nadu region by and the number of reported cases changed every year.

The maximum dengue incidences were reported in the year 2012 (n = 15,770) and the minimum in the year 2008 (n = 565). There was a 175% increase every year, until 2011[20,21,22]. But there was a threefold increase in the year 2012 when compared with the earlier years. As per IDSP records highest number of cases have been documented from Viluppuram district (226 cases) in 2010, Puducherry (152) in 2011 and Puducherry (1600) after that Tirunelveli (1365) in 2012. But, the number of deaths were very low when compared with the number of cases reported in 2010 and 2011; but the number of deaths were far above the ground (40) in 2012, particularly from the Tirunelveli district (32 deaths).[25,26,27]

In 2015, a major outbreak happened in India. Almost all states were affected, especially Delhi and Punjab. As per NVBDCP Punjab, Delhi, Haryana West Bengal, Maharashtra and Gujarat had 15000, 15000, 8000, 7000, 4000, and 5000 confirmed cases respectively. Total reported cases in 35 states were 90,000 and the total mortality was 180, up to 30th Nov 2015.

Table 3.1: Year wise dengue cases in India

Year	Cases	DEATHS
2009	15500	96
2010	28300	110
2011	18860	160
2012	50200	290
2013	75800	195
2014	40570	190
2015	90090	180

Dengue virus and its serotypes

Dengue virus belongs to Flavivirus group. It is a single stranded RNA virus. The infection is transmitted by mosquito bite .So it is an arthropod borne virus (arbovirus)[31,32]. It is a single stranded RNA virus with an icosahedral nucleocapsid, a lipid envelope and three structural proteins (envelope protein-E, core protein-C, and membrane associated protein-M) and non-structural proteins(NS1,NS2A,NS2B,NS3,NS4A,NS4B and NS5)[33,34,35].

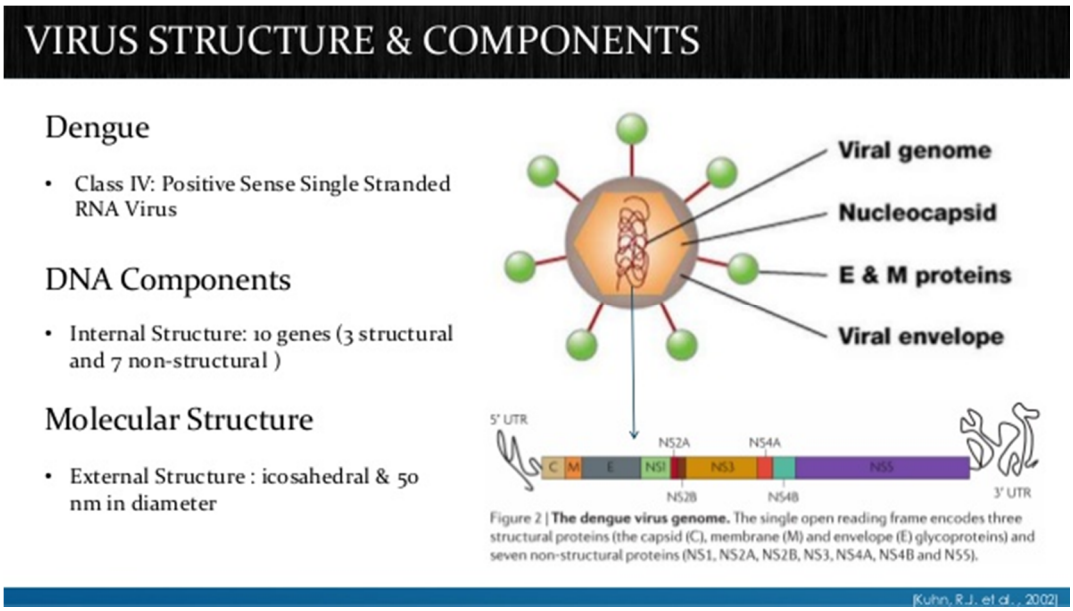


Figure 3.3: Structure and components of dengue virus

Five serotypes of dengue viruses are causing human infection-DEN1, DEN2, DEN3, DEN 4, DEN5.[36,37] There is only transient cross immunity between the five serotypes. So people in dengue endemic areas may get dengue infection up to five times during their life time[38,39,40]. Previously 4 serotypes were known and recently in 2013 the 5th serotype identified.

Epidemiology of dengue

Epidemics caused by dengue virus have been known since 1780's [41]. It is having worldwide distribution and endemic in more than tropical and subtropical countries. WHO estimates about 50-100 million cases of dengue fever every year world wide .[42,43]

The virus causing Dengue fever was first isolated in Japan in the year 1943 by inoculating serum of DF cases in suckling mice and at Kolkata (old

Calcutta) in 1944from blood samples of US soldiers[44]. The earliest clinical dengue epidemic was reported in Chennai (old Madras) in the year 1780 but the first microbiologically proven epidemic of Dengue Fever in India happened in Kolkata and the Eastern Parts of the country in 1963-1964[45,46].

The first main DHF epidemic was recorded in Philippines in 1953-1954[47]. Dengue Hemorrhagic Fever had its incidence in the nearby countries but it was not seen in our country because of unknown reasons even though all the favouring conditions were there. The DHF was diagnosed in many areas of our country since 1988[48,49,50].

Mode of Transmission

Infection is transmitted by the bite of mosquito. Aedes aegypti mosquito is the main vector[51], Aedes albopictus playing a secondary role. Four cases have been documented in history by the percutaneous transmission through needle prick injury [52]. Infection with one serotype of virus does not provide lasting immunity against other serotypes. When a different serotype virus infects a person for a second or third time, it results in severe dengue (DHF and DSS)[53,54,55].

The principal vector, Aedes aegypti mosquito is a highly domesticated tropical mosquito. It lays eggs in artificial water containers commonly found in and around human dwelling. Aedes breeding is demonstrated in discarded coconut shells and plastic containers in rubber plantations. The metallic or

plastic containers located at the base of refrigerators in houses also supports breeding of Aedes albopictus[58]. Aedes albopictus breeding was found in the leaf axis of many plants .The adult mosquito rests in doors and prefers to bite humans during day with peak biting activity in the early morning and late afternoon hours. The adult female mosquitoes are voracious feeders and if their feeding is interrupted, they return to the same person or a different person to continue feeding. So during a single blood meal, several persons may get infected making Aedes aegypti a highly efficient vector. The transmission cycle is –Aedes aegypti-human-Aedes aegypti in large urban centres of tropics.

Figure 3.4 : Aedes aegypti taking a blood meal.

Immuno -Pathogenesis

All four serotypes can cause infection. Infection with one serotype shows immunity to that serotype but does not provide long-term cross-protective immunity to the other serotypes. Severe disease is seen especially in patients having a second or subsequent infection with a dengue serotype different from the first infection, or else in infants with transmitted maternal antibody having their first infection. The antibody-dependent enhancement (ADE) hypothesis suggests that the residual heterotypic non-neutralizing antibodies bind to the new virus promoting its infectivity by increasing the efficiency of binding and uptake of virus-antibody complexes through Fc receptors on blood monocyte or tissue macrophage cells, thus amplifying viral replication. The resulting increase in viral load drives an immunopathogenic cascade that alters microvascular function in some way, resulting in capillary leakage and coagulopathy. Rapid mobilization of serotype cross-reactive memory T cells has been suggested as an alternative mechanism to trigger the inflammatory cascade.

Differences in viral virulence, molecular mimicry, and immune complex and/or complement-mediated dysregulation, as well as age and genetic predisposition are other factors considered to influence disease severity. But, the pathogenesis of the vascular leakage and coagulopathy remains poorly understood and, so far, no mechanism has been identified that links the

established immunological derangements with a definitive effect on microvascular structure or function.

Effect of Dengue virus infection on megakaryocytes and platelets

Dengue virus sero type 2 not only blocks megakaryopoiesis but also causes apoptosis in a minor population of early megakaryocytic precursors that can lead tothrombocytopoenia[59]. In a different study it was shown that Dengue virus-2 can cause platelet activation and can lead to thrombocytopenia[60].

Capillary leakage in DV infection

Severe infection of dengue is causes capillary leakage, leading to accumulation of fluid in the body cavities. Many studies have been done to identify the mechanism of the above phenomenon. It has been shown that inoculating CF/CF2intraperitoneally in mice leads to increased vascular permeability. Peak leakage happens 30 minutes after inoculating CF and the vascular integrity is returns back to normal within 2 hours. The raise in vascular permeability is abolished by pretreatment of mice using anti CF antibodies, Chlorpheniramine maleate (H1antihistamine) or Cimetidine (H2 antihistamine) [63,64]. CF isolated from pooled serum of Dengue patients on inoculating intravenously into mice raised vascular permeability and disrupted the BBB (blood brain barrier)[65].

CF & CF2 are suggested to the pathogenesis-related proteins related to pathogenesis which may produce DHF-like pathology in mice like capillary leakage, blood leucocyte changes and cerebral edema[63,64,66,67,68..]Immunising mice using CF will protect them from further attack by CF, while challenge of such mice using a lethal intra cerebral dose of Dengue virus help in preventing only the clinical features but it does not prevent death[69]. With utility of endothelial cell monolayer models appreciable job have been made recently to suggest the patho physiology of capillary endothelium during infection with dengue virus result in leakage of plasma as observed in very severe dengue disease.[70,71,59]

Pathogenesis of DF/DHF

One among the very important aspects of dengue research understands the factors which are contributing in the pathogenesis of Dengue Hemorrhagic fever. It was suggested that DHF is due to a "Cytokine Tsunami". But in spite of large scale studies for many years; its pathogenesis is yet not completely known. The process resulting in DHF/DSS are Antibody-Dependent Enhancement (ADE)[72], T cellresponse[73,74,75], as well as a change from Th-1 to Th-2 response76. These altogether leads to cytokine tsunami[77] leading to flow of body fluids into extravascular compartment. It has been discovered that a Th 1 response leads to recovery from infection and a Th2 response is linked to severe illness and exacerbation of the disease in dengue infection[76,78]. The role of Thl 7 cells in pathogenesis of dengue have been looked and warrant serious

attention by researchers[79]. CF/CF2 causes macrophage activation leading to release of free radicals, nitrite, peroxynitrite and reactive oxygen species [80,81,82]. The free radicals, not only cause apoptosis of the target cells but also directly up regulate synthesis of pro-inflammatory cytokines; tumour necrosis factor (TNF)-alpha, interleukin-1 (IL-1), interleukin-8 (IL-8), and hydrogen peroxide in macrophage.[78,83,84] This leads to oxidative stress. Plasma protein carbonylation, protein carbonylation to protein-attached sulphydryl group ratio are suggested to predict DHF/DSS[85,86]. The elevation in relative concentration of IL-12 and transforming growth factor (TGF)-beta shifts a Thl-dominant response to a Th2 biased response leading to severe dengue disease. The increase in capillary permeability is attributed to synergistic effect of cytokine tsunami, free radicals, release of histamine and the products of the complement system activation, etc. So the major actor is CF/CF2, but the activity is moderated by CF-autoantibodies produced in patients with denguedisease[87].

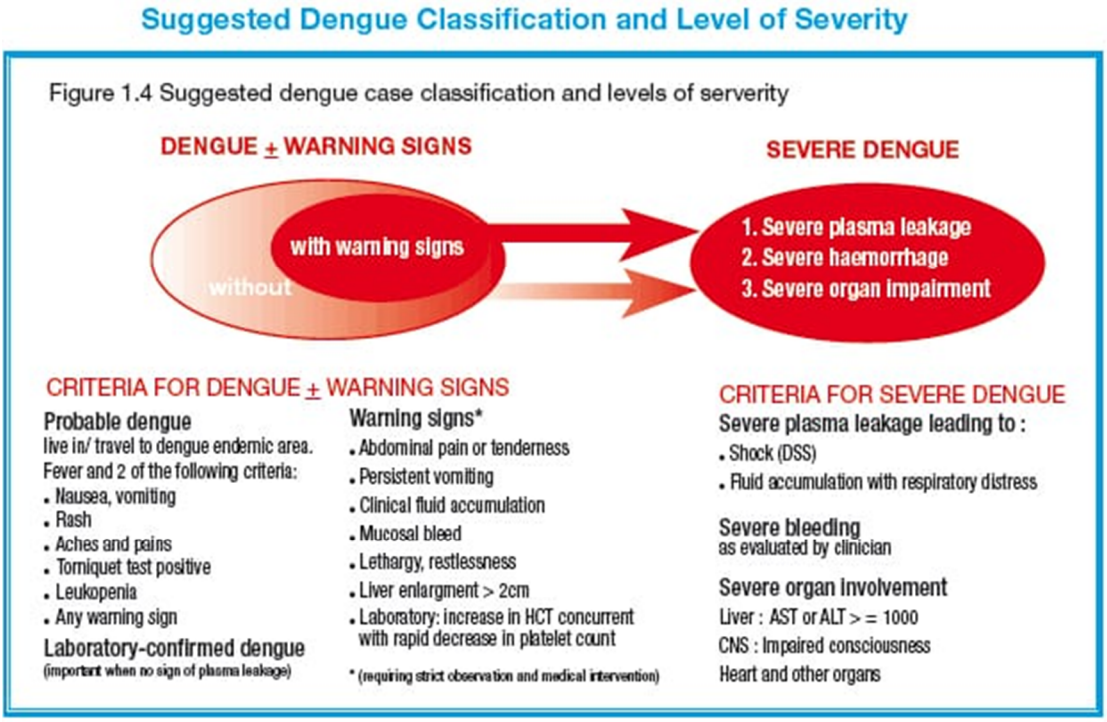
The contributing factors discussed periodically are dengue virus non¬structural protein type 1 (NSl)-antibodies that cross-react with vascular endothelium (an autoimmune phenomenon), immune complex deposition, memory Tcells, complement and its products, various soluble mediators including cytokines assortment of virulent strains and virus virulence etc.[77,88,,89.] Also, DV has the capacity to escape the innate immune mechanisms of the host by preventing both typeI interferon (IFN) production and signalling in many human cells, including dendritic cells (DCs). The virus also produces proteins

that block type I IFN signalling,including NS2A, NS4A, NS4B and NS5 by targeting various components of this signalling pathway, such as STATs. This adds to the immuno-pathogenesis and host tropism of this virus[90]. Further, there is a critical role for invariant natural killer (iNK)T cells in mice[91]; altered plasma levels of vitamin D and mannose binding lectin[92];shift from Thl cytokine to Th2 cytokine expression; role of saliva of Aedes egypti[93];and intracellular variations in host proteins[94] were reported. Two loci on chromosomes six and ten have been discovered which are related to susceptibility toDSS[95.] Classical and non-classical HLA alleles have been linked to be related with disease severity in the host[82,96,97]. Additional mechanisms are Dengue Virus utilizes calcium modulating cyclophilin-binding ligand to weaken the apoptotic process that leads to well-organized virus production[98]. An association between increased lipopolysaccharide levels and the severity of the disease has also been reported[99].

Clinical Features

Dengue infection causes a wide variety of illnesses ranging from subclinical infection to short febrile illness to very severe & fatal disease. Many infections are clinically asymptomatic. Previously, symptomatic disease was divided into 2 major clinical syndromes, dengue fever (DF) and dengue haemorrhagic fever (DHF), with case definitions and management policies for them published by the World Health Organization (WHO).

It was in 1974 the WHO case definition of dengue into dengue fever (DF)/dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) was prepared by the Technical Advisory Committee in Manila, Philippines[100]. The distinctive feature of DHF is vascular permeability increase, which can result in hypovolemic shock. To diagnose DHF, there must be some evidence of bleeding and platelet count should be less than 100 x 10^9/litre.



Source: World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009

WHO criteria for DHF; all of the following four must be present

- Fever or history of acute fever lasting for 2 to 7 days.
- Bleeding manifestations in the form of at least one among the following: a positive tourniquet test, petechiae, ecchymosis, purpura, mucosal

bleeding, sites of injection or any other location; gastrointestinal tract-haematemesis and/or malena.

- Thrombocytopenia (100,000 platelets or less).

- Hemoconcentration (20% or more increase in the haematocrit (PCV) value comparative to the baseline average for the same age and sex of the individual) or evidence of plasma leakage in the form of pleural effusion, ascites and/or hypoproteinaemia.

Setiati et al. uses 6 modified classification systems, other than the WHO classification system, to identify patients in shock. Since fever was present in all patients; the other three features (bleeding manifestations, thrombocytopenia, and signs of plasma leakage) were used to make the modifications. This led to the six classification systems as given below: hemorrhagic manifestations and thrombocytopenia; hemorrhagic manifestations and haemoconcentration; haemoconcentration and thrombocytopenia; hemorrhagic manifestations and thrombocytopenia or haemoconcentration; thrombocytopenia and haemoconcentration or hemorrhagic manifestations; and lastly, haemoconcentration and hemorrhagic manifestations or thrombocytopenia. The sensitivity for the detection of patients with shock of WHO classification system is 86%. All modifications made to the WHO classification system have more sensitivity than the WHO classification system (sensitivity varies from 88% to 99%>)[101]. Therefore, we

can assume that Dengue Fever and Dengue Hemorrhagic Fever are actually the part of a spectrum of common illness rather than two different entities[102.]

Also, WHO's DHF / DSS classification does not include severe dengue infection presenting with "uncommon manifestations " like encephalopathy and frequently encephalitis, hepatocellular failure, cardiomyopathy & myocarditis, dengue fever with serious hemorrhagic manifestations and ARDS[103]. These uncommon presentations, those are not recognized by the WHO's case definition criteria, are never uncommon in endemic areas like India[104, 105.]

Because of practical difficulties, a revised classification system was developed, based on prospective data obtained from over 2000 patients with dengue infection from endemic areas all over the world, and this has now been taken in the newer WHO guidelines for dengue published in 2009. The new scheme divides the disease into dengue and severe dengue, in line with several other complex diseases such as malaria and pneumonia. It is expected that in the future this will be a simpler system that may be useful for triage, aid in clinical management, and improve the quality of surveillance and epidemiological data.

Symptomatic dengue is mainly a disease of older children and adults. The symptoms start suddenly after an incubation period of 4 to 7 days and typically characterised by three phases—an initial febrile phase, a critical phase around the time of defervescence, and a spontaneous recovery phase.

Febrile Phase

There is sudden onset of high grade intermittent fever along with facial flushing, headache, retro-orbital pain, lumbosacral pain, severe malaise, myalgias ,bone pain, anorexia, altered taste, mild sore throat, nausea, and vomiting. Younger children can experience high fever, but are usually much less symptomatic. A few patients may be having a transient rash or skin mottling in early phase of the disease.

Other findings of dengue infection include generalized lymphadenopathy, mild haemorrhagic manifestations and palpable hepatomegaly but rarely splenomegaly.

Haematuria is rare & jaundice is uncommon. Laboratory findings during the early phase of the disease include leukopenia and thrombocytopenia, often with some elevation of hepatic amino transferases.

Critical Phase

Majority of patients will recover by the time of defervescence, usually between 3-7 days of the disease, but in a minor proportion, an increase in capillary permeability becomes severe, complicating the critical phase. The capillary leak syndrome is characterised by increasing haemoconcentration, hypoproteinaemia ,ascites and pleural effusions, and, in severe cases, it may compromise the circulating plasma volume causing the potentially life-threatening dengue shock syndrome(DSS). The patient is defined as having

DSS when the pulse pressure narrows to less than 20 mmHg with a rapid weak pulse and impaired peripheral perfusion, or if hypotension develops. If prompt fluid resuscitation is not given, the ongoing depletion of plasma becomes critical, the systolic blood pressure falls rapidly, and irreversible shock and death can occur. But, with careful fluid management most of the patients make a full recovery. Warning signs that indicates the severity of the disease include intractable vomiting, severe abdominal pain, and increasing hepatomegaly. Haemorrhagic manifestations that are seen during this phase include skin petechiae or bruising, or a positive tourniquet test. Mucosal bleeding (e.g. epistaxis, gastrointestinal bleeding, haematuria, menorrhagia) can occur, but are rarely clinically important in children except in combination with severe shock. However, adults have a tendency to have more severe hemorrhagic manifestations than children; gastrointestinal bleeding and menorrhagia can be significant even in cases with minimal evidence of vascular leakage. Moderate to severe thrombocytopenia is usual, with platelet count below 20 x 10^9 /litre often seen during the critical period which rapidly improves in the recovery phase. A prolongation in the activated partial thromboplastin time and a reduction in fibrinogen levels are commonly noted. Eventhough, the above findings are not suggestive of classic disseminated intravascular coagulation, the true nature of the coagulopathy is not known. Other laboratory investigations show similar abnormalities.

Recovery Phase

The increase in vascular permeability is transient and comes to normal after 24- 48 hours. Reabsorption of fluid occurs rapidly and is often associated with an obvious diuresis, leading to clinical improvement. There may be a second scarlatiniform to maculopapular rash, which may appear around day 6 to 7 of disease, mainly on the extremities and sometimes involves the trunk and face. The rash blanches on deep pressure, can be associated with intense pruritus, and very often resolves with desquamation.

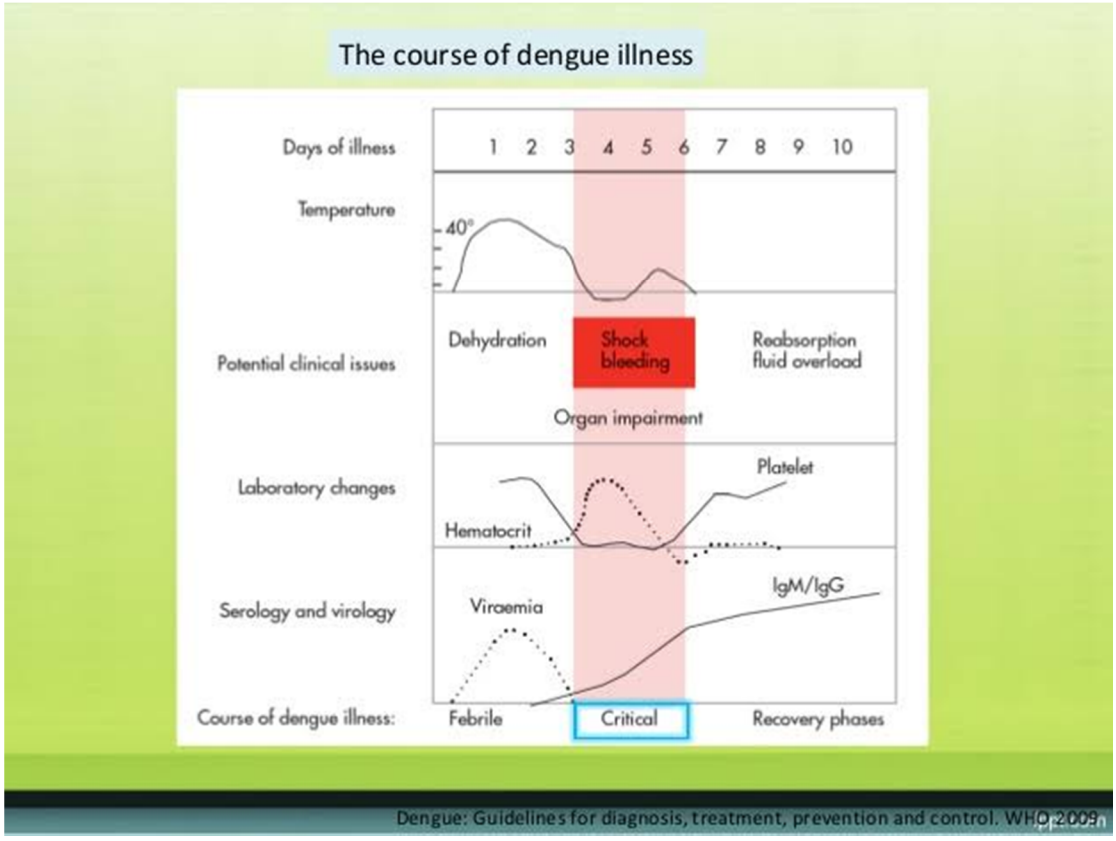


Fig. 3.6 Course of dengue illness

Dengue fever and the Hepatobiliary system

The involvement of liver in dengue fever is not rare. It has been reported in literature since 1970[112]. In the Liver Function Tests (LFT) the commonest abnormality detected is elevated amino-transferases. Aspartate Amino-transferase (AST) is higher than the Alanine Aminotransferase (ALT) in about 90% ofcases[113,114]. DF causes the inflammatory responses leading to hepatic parenchymal changes, releasing aminotransferases into the circulation[115]. Deranged liver function tests are seen in patients with dengue infection due to direct attack on the hepatocytes or unregulated host immune response against the virus[116]. So there is a need for monitoring liver function tests[117]. The patient may complaint of right hypochondrial discomfort and pain. Tender hepatomegaly is seen in many cases. Ultrasound examination is also useful. Even though DHF can cause mild to moderate hepatic dysfunction in majority of cases, only a few patients suffer from fulminant hepatic failure resulting in encephalopathy and death [118]. Encephalopathy is an uncommon complication of dengue infection which may be due to hyponatremia, intracranial haemorrhage, cerebral oedema, cerebral anoxia, fulminant hepatic failure with hepatic encephalopathy, microcapillary haemorrhage or release of toxic products[119]. Inpatients having encephalopathy, serum ammonia and hepatic amino transferase were elevated suggesting liver cell failure with hepatic encephalopathy as the cause of CNS manifestation.

Liver derangement with elevated levels of aminno transferases similar to those caused by hepatitis virus has been observed in patients with dengue[120]. Liver injury due to dengue virus is caused by its direct infection of hepatocytes and kupffer cells . The mortality rate is extremely high in patients with hepatic encephalopathy.

Dengue –CNS manifestations

Neurological manifestations include headache, seizures, coma, neck stiffness, raised intra cranial tension, myoclonus, encephalitis; behavioural disorder. Post infection sequale may persist as dementia, depression, psychosis, extrapyramidal effects. Rare neurological manifestations are intracranial bleeding, cerebral edema, hypoxic encephalopathy, etc. Dengue virus can cause encephalopathy or encephalitis [106,107].Dengue encephalitis can be definitely diagnosed by brain biopsy. Imaging can be used as supportive evidence. In addition to encephalitis, rarely reported neurological complications include mononeuropathies, polyneuropathies, AIDP, GBS, transversemyeltis.[108,109]

Dengue and Hematopoietic Parameters

Hemoconcentration and raised hematocrit are seen commonly in DHF. Decrease in leukocyte count, particularly neutrophil, thrombocytopenia, and atypical lymphocytes are other common findings. During convalescence eosinophilia and basophilia may occur. This may be due to recovery from bone marrow suppression. The reasons for thrombocytopenia in dengue include

direct bone marrow suppression, destruction of megakaryocytes or developing antibodies against platelets. Coagulopathy is also not rare in severe dengue. It was found that aPTT prolongation is more common than PT prolongation in dengue patients. Decreased fibrinogen concentration is seen in certain cases.

Dengue and the Renal System

A variety of renal disorders are seen in dengue, adequate studies are not available regarding that. Acute renal failure, proteinuria and glomerulonephritis have been reported.

Acute Renal Failure:

Acute renal failure is a serious complication of severe dengue and it may be due to hypotension, rhabdomyolysis or hemolysis. Indian studies suggest that acute renal failure complicates severe dengue infection in 2 to 5% of cases and it is associated with a high mortality rate. Some other series in India shows that prevalence of acute kidney injury ranges from 0.2 to 10% in paediatric patients and 2.2 to 35.7%in adult patients with dengue infection.

Proteinuria:

Proteinuria is detected very frequently in dengue hemorrhagic fever patients .But nephrotic range proteinuria reported only in few case series. Spontaneous remission of proteinuria is the rule.

Glomerulonephritis:

There have been many reports describing the various types of glomerulonephritis in dengue infection. Electron microscopic demonstration of IgG,IgM and C3 deposits and thickening of glomerular basement membrane are reported.It is observed that the size of immune complex is smaller than that of glomerulonephritis. The chances are more in those with already existing renal disease.

Hematuria:

There are reports showing asymptomatic proteinuria in up to 12.5% patients with dengue hemorrhagic fever. The reasons include either thrombocytopenia or acute glomerulonephritis or Buerger's disease.

Others:

Mild elevation in serum creatinine is reported in 43% of dengue hemorrhagic fever cases in a Thailand based study done by Futrakul et al. transient azotemia has been reported by Tanphaichitr et al, an isolated case of haemolytic uremic syndrome have been reported.

Dengue Fever and Cardiovascular System:

Now days, cardiac involvement is seen more frequently in dengue fever patients. The cardiovascular manifestations are largely not known because most of the cases are asymptomatic and have a self -limited course. The most

common cardiovascular manifestation is myocarditis leading to dilated cardiomyopathy [110,111]. AV block, atrial fibrillation, sinus node dysfunction and ventricular premature beats have been reported in dengue infected patients. Myocarditis should be suspected if a dengue fever case presents with refractory shock and congestive cardiac failure. The myocarditis is reported less because most patients are not investigated for the same. It is often missed. The mechanism of myocarditis may be direct viral infection and immune complex deposition in myocardium.

Cardiac rhythm abnormalities such as sinoatrial block, first degree and mobitztype1 second degree AV block and atrial premature contractions/ventricular premature contractions. Spontaneous remission is the rule in most of the rhythm abnormalities. Even though dilated cardiomyopathy is a serious complication it can occur rarely. Prompt clinical suspicion, early diagnosis and management of congestive cardiac failure can save the life of the patients.

Dengue and the respiratory system:

Complicated dengue can have pulmonary manifestations. Pleural effusion, pneumonitis, pulmonary haemorrhage and hemoptysis have been reported. Acute respiratory distress syndrome may occur in dengue hemorrhagic fever and dengue shock syndrome. The case fatality rate increases with pre-existing lung diseases like bronchial asthma and COPD.[112]

Dengue and the lymphoreticular system:

Dengue virus has been demonstrated in spleen, lymph node and thymus. Splenic rupture is a rare complication. Abdominal pain is the main presenting symptom. The commonest differential diagnosis is acalculous cholecystitis. Profound hypotension is the rule in such cases.So whenever any febrile patient in a dengue endemic zone presents with fever,abdominal pain and hypotension suspicion of splenic rupture is mandatory. Early diagnosis and splenectomy may save the patient.

Dengue and musculoskeletal system:

The alternative name break bone fever describes the muscle, joint and bone pain in dengue fever. Rhabdomyolysis has been rarely reported in dengue. To identify the same, urine should be screened for Haem and CPK levels must be estimated. This may possibly happen due to myotoxic cytokines especially TNF-Alpha. Histopathological examination may show foci of lymphocytic infiltration and myonecrosis. Patient can present due to pure motor weakness or quadriplegia, the weakness and pain may persist even after recovery, a short course of steroids may be helpful in such cases.

LIVER FUNCTION TESTS

S.Bilirubin

The total serum bilirubin can be elevated in both hepato-cellular and cholestatic diseases with an associated increase in hepatic enzymes. In the cholestatic cases the conjugated bilirubin is mainly elevated. An isolated mild increase in serum bilirubin (with normal enzymes) may be genetic or because of haemolytic diseases.

Hepatic Transaminases

Serum glutamate oxaloacetate transaminase (SGOT or Aspartate amino-transferase :AST) is a mitochondrial enzyme that is present in heart, liver, kidney and skeletal muscle, and the serum level is elevated in acute destruction of the above mentioned tissues, probably released by the damaged cells. Serum glutamate pyruvate transaminase (SGPT: Alanine aminotransferase: ALT) is a cytosolic enzyme present in the hepatocytes. Even though the net amount is less than SGOT, a greater proportion is found in the hepatocytes on comparing with heart and skeletal muscles. So an elevation of SGPT is more specific for hepatic injury than SGOT[123,124,125]. Aminotransferase estimations can be used for diagnosing viral hepatitis.

Measurements should be done early, because values reach to normal within a few days of the starting of the disease[127]. The patient can have severe acute liver cell necrosis despite reducing aminotransferase levels. The most

common causes for SGOT being more than ten times the higher limit of normal are ischaemic hepatitis, viral hepatitis, Toxins and drug induced hepatitis.[129] A high ratio (deRite's ratio) of SGOT to SGPT (greater than two) is used to diagnose alcoholic liver disease. This is because of both hepatocyte damage and pyridoxal 5- phosphate (vitamin B6) deficiency.

Enzymes reflecting cholestasis

Alkaline phosphatise (ALP) 5' nucleotidase, and gamma glutamyl transferase(GGT) are generally increased in cholestasis. Alkaline phosphatase and 5'-nucleotidase are seen in or near the biliary canalicular membrane of liver cells, while GGT is found in the endoplasmic reticulum and in the epithelial cells lining bile duct.

Severe Dengue

As per the modified scheme, the patients who recover without any complications are labelled to have dengue, while those who suffer from any one of the following problems are labelled to have severe dengue: plasma leakage leading to shock and/or fluid accumulation sufficient enough to cause acute respiratory distress; severe hemorrhagic manifestations; severe organ involvement, e.g. liver failure, myocarditis etc. But majority of deaths due to dengue is seen in patients with profound shock, especially if fluid overload complicates the situation.

Differential Diagnosis

The differential diagnoses are influenza, leptospirosis, typhoid, malaria,Epstein-Barr virus, measles, rubella, rickettsial infection, other arboviral infections with rash, other viral haemorrhagic fevers, and meningococcemia.[126,128]

Diagnosis:

In the early febrile phase (up to about 5th day of the disease) laboratory diagnosis of dengue fever depends on virus isolation or detecting viral antigen or viral RNA by reverse transcription-polymerase chain reaction (RT-PCR) in blood. After this phase IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA)is the most commonly used serological test for diagnosis of dengue; seroconversion or an increasing titre of specific dengue IgM or IgG in paired serum samples is suggestive of acute infection. Secondary infection cases (dengue or other flavivirus infection) usually develop high titres of IgG antibodies in the acute phase and the intensity of IgM response may be less. IgM may be false positive in other flavivirides-JE, non flavivirides-malaria, leptospirosis, toxoplasmosis and syphilis, connective tissue disorders-rheumatoid arthritis, chronic liver disease. Serological diagnosis is also complicated due to the presence of flavivirus cross-reactivity, creating it essential to do tests for other locally prevalent flaviviruses along with dengue serology. Since antidengue antibodies remain for many months, diagnosis

depending on a single positive MAC-ELISA result must be taken provisional. Rapid diagnostic serological tests are now available but they also may not become positive until towards the end of the first week of the disease. ELISA test to identify circulating dengue nonstructural protein 1 (NS1 antigen) during the earlier days of disease may be used for early diagnosis.

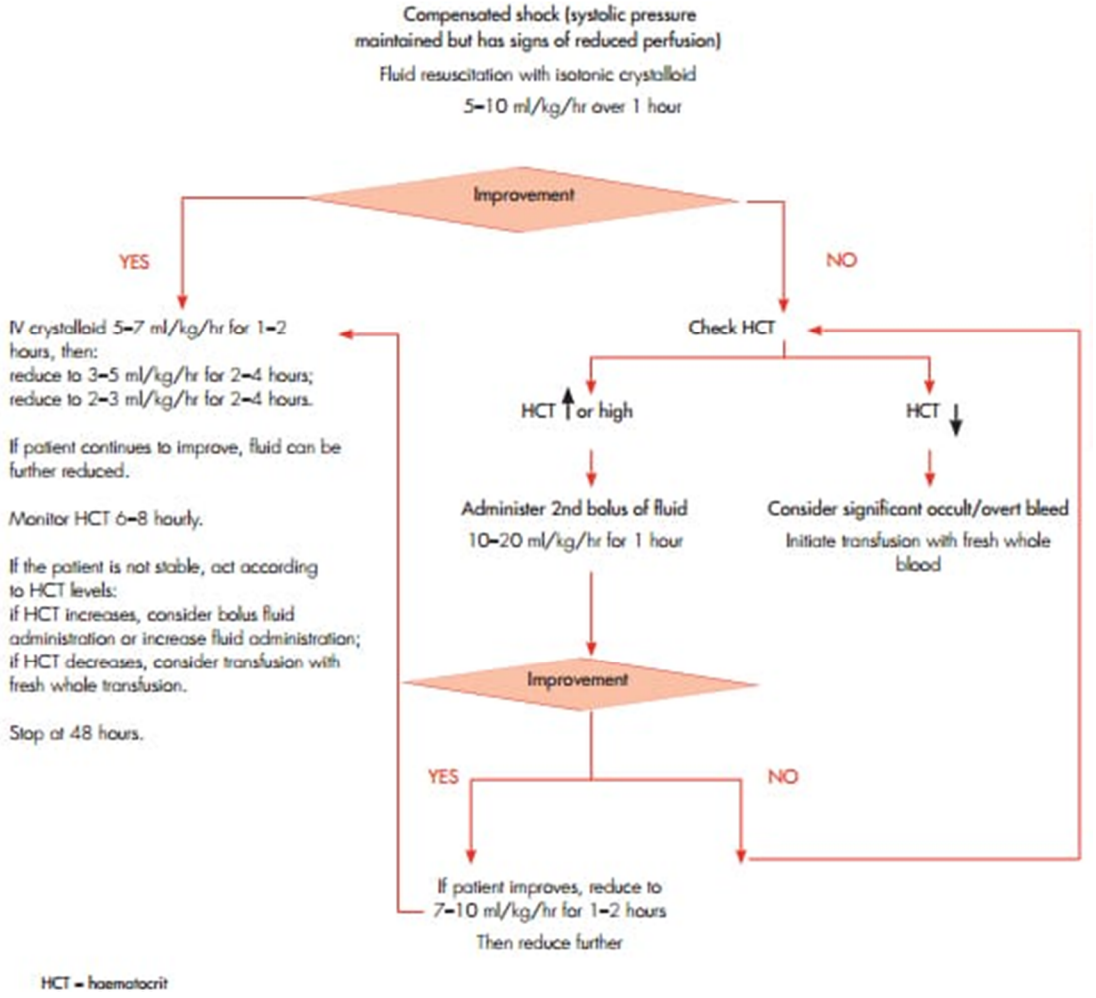
Figure 3.7:- Rapid Dengue IgM/IgG Combo ELISA Test Card.

Treatment

General supportive measures, with special focus on judicious fluid management, remain a must for a better outcome. Oral rehydration is usually enough for patients having mild disease. Antimicrobial therapy is not yet

available for treating dengue, even though many viral inhibitors are in preclinical trials. No ancillary drugs have been shown to have a benefit. Corticosteroids don't have a convincing benefit on mortality from shock in many clinical trials, but whether their use before the occurrence of shock influences outcome is still not known.

Fever can be managed with tepid sponging and paracetamol. Aspirin and other non-steroidal anti-inflammatory drugs are contraindicated.



Criteria for hospitalization

- Abdominal pain and tenderness
- Persistent vomiting
- Volume overload features
- Mucosal bleed
- Lethargy or restlessness
- Liver enlargement >2cm
- Increasing haematocrit and decreasing platelets

Intractable vomiting, mucosal bleeding, severe abdominal pain, or severe skin bleeding, a rapidly increasing hematocrit, or a marked fall in the platelet count suggest the need for close observation and monitoring of vital signs and hematocrit.

When to do complete hemogram?

- all patients with fever >3days
- all patients with confirmed dengue fever daily
- all patients in shock - 4 to 6 hourly

Judicious use of intravenous fluids is needed for patients with a rapidly increasing hematocrit. For DSS cases, sudden but judicious restoration of circulating plasmavolume is important, followed by maintenance fluids to support the circulation sufficient to maintain organ perfusion until vascular permeability becomes normal. But still, fluid overload with respiratory compromise is a usual complication and one among the important contributors to mortality. So the amount of intravenous fluid given should be kept to the minimum enough to maintain cardiovascular stability and sufficient urine output during the phase of vascular leakage, and as soon as reabsorption starts, usually about 1 to 2 days later, intravenous fluids may be stopped.

Isotonic crystalloid solutions can be used in the initial phase. Colloid solutions can be given for patients having severe DSS and those who do not respond to crystalloid therapy.

Correction of metabolic acidosis, electrolyte abnormalities, and hypoglycaemia are also important. Platelet concentrates are not indicated, even for severe thrombocytopenia unless there is severe bleeding, as the thrombocytopenia settles rapidly during the recovery phase of the disease without any active treatment**.**

For patients with petechial bleeds/mild mucosal haemorrhages but hemodynamically stable, supportive care (Bed rest, fluids, monitoring) is only required, avoiding IM injections. **THERE IS NO EVIDENCE TO**

SUPPORT THE USE OFPLATELET CONCENTRATE OR FFP OR CRYOPRECIPITATEWHATEVER BE THE SEVERITY OF THE BLEED. However, when there is severe bleeding with hemodynamic instability, transfusion of fresh whole blood, or packed cells may be of value, but should be given with at most care due to the risk of volume overload. If bleeding continues and is uncontrollable, DIC has to be considered.

CRITERIA FOR DISCHARGE

- absence of fever for at least 24 hours without the use of any anti-fever therapy
- return of appetite
- visible clinical improvement
- satisfactory urine output
- minimum of 2-3 days have elapsed after recovery from shock
- no respiratory distress from ascites and pleural effusion
- platelet count >50,000 for at least two days

(Avoid traumatic activity for two weeks since platelet count will become normal by this time only)

Most patients with dengue infection make a complete recovery. Patients with DSS and/or major bleeding usually do respond provided they are given adequate supportive care from experienced hands during the critical phase of the disease.

Adults may have several days of severe fatigue, weakness, pruritus, skin desquamation, and depression during convalescence phase, but there permanent sequelae are not there. In general, children recover more rapidly and may not have such complications.

RECENT ADVANCES IN THE MANAGEMENT OF DENGUE FEVER

Herbal Treatment

The aqueous extract of papaya (Carica Papaya) leaves are proposed to have therapeutic effects due to many active components like papain chymopapain, cystatin, cyanogenic glucosides and glucosinolates. The above mentioned compounds are antioxidants that reduce lipid peroxidation, exhibit anti tumour activity and immunomodulatory effects. There are many south Indian studies which suggest that Carica Papaya Leaf Extract (CPLE) does significantly increases the platelet count in dengue patients. There is a need for high quality trials regarding the same.

Antivirals

No specific antiviral drugs are available at present. However there have been many attempts to discover one. Ribavirin, Glycyrrhizin and 6-Azauridine are reported to have anti-dengue virus effect. Adenosine analogues like NITD008 is one of the currently being studied drug.

High dose IV immunoglobulin

It has been tried in several trials, and conflicting results are there. Recent studies suggest that the immune-mediated platelet destruction and vasculitis in dengue fever are caused by immune complexes. The exact mechanism of action of IV Ig is not well understood.

Corticosteroids

There is scarcity of good evidence regarding the effect of steroids in dengue.

WHO do not recommend corticosteroids for the treatment of dengue fever. It is a matter of controversy.

Monoclonal antibodies

VIS513 is a monoclonal antibody that targets a conserved region on dengue virus. Preclinical studies have shown that it neutralises all the 4serotypes of dengue virus, and gives protection after a single systemic administration.

DENGUE VACCINES IN CLINICAL DEVELOPMENT

Figure 3.9: Dengue Vaccine

Sanofi Pasteur's CYD vaccine

It is a tetravalent chimeric live attenuated vaccine which is administered subcutaneously. Trials are ongoing regarding the use of this vaccine. Some studies suggest the dosage schedule as 0, 3,5, and 12 months while certain others suggest 0, 6and 12 months schedule.

DEN Vax (Inviragen/ Takeda)

It is a candidate vaccine which can be administered either subcutaneously or intradermally.

TV003/ TV005 (NIAID)

It is a vaccine developed by the National Institute of Allergy and Infectious Diseases by incorporating potential vaccine strains into their tetravalent dengue vaccine candidate.

TDENV PIV (GSK)

It is a tetravalent purified inactivated vaccine.

Virus like Particles Using Pichia Pasteuris

A group of scientists developed DENV envelope (E) protein-based virus like particles (VLPs) without premembrane protein (prM) (implicated in the induction of disease enhancing antibodies) using methylotrophic yeast Pichia pasteuris . This has lead to the development of a non- replicating, safe, efficacious and affordable dengue vaccine. In extension of this approach, prM-lacking DENV -3EVLPs have been produced using Pichia pasteuris. Animal studies are ongoing regarding the virus-like particles using Pichia pasteuris. Finally, there is no recognized correlate of protection for a valuable dengue vaccine. Currently immunogenicity researches to measure neutralising antibodies for all 4 serotypes of dengue virus are needed to move forward with a vaccine candidate.On account of the severity of the dengue problem, many of the above vaccine candidates are required to guarantee an adequate vaccine supply in the long term future. Many more works are required to be made to establish the use of dengue vaccine. Mathematical modelling has proved that a vaccine with specific features would be much useful in decreasing overall dengue infections in population that receive such a vaccine overtime by routine vaccination of children with a single catch-up campaign in older children, and possibly adults. In future, we can hope that an effective vaccine maybe developed in the future to reduce the burden of the disease.

Prevention of Dengue Fever

Even though many efforts are being put towards discovery of safe and effective dengue vaccines, it doesn't seem that an appropriate candidate may be available for large-scale deployment for many years. Until then prevention of dengue epidemics will continue to depend upon elimination of potential vector breeding sites along with biological and chemical vector control strategies.

Community control of Aedes aegypti by eradication of mosquito larvae from stagnant water sources is recommended but it's very difficult to achieve in contemporary tropical urban areas. Since Aedes aegypti mosquitoes are predominantly daytime biters insecticide-treated bed nets have not much use. Avoidance of mosquito bites in areas infested with Aedes aegypti by using mosquito repellents containing N, N-diethyl-3-methylbenzamide (DEET) or picaridin and protective clothing are the most important preventive measures for the traveller.

Previous Studies

Vaibhav Shukla et al conducted a study named " A Study of Hepatic Dysfunction in Dengue",in medicine wards at Eras Lucknow Medical College from August 2010 to November 2010.[130] 70 IgM Dengue positive patients were included in the study.100 % had an elevation in SGOT while 91% had an elevation in SGPT.85% had SGOT levels more than 2 times normal ,while 48% had SGPT >2 times normal. In patients

who had raised levels of both enzymes, SGOT levels were 2-3 times higher than SGPT levels. Elevation in SGOT levels was seen as early as day 2 or day 3 of fever.

Jagadishkumar K et al conducted a study titled "Hepatic Involvement in Dengue fever in children".[131] 110 children with serologically positive dengue feveraged between 2months to 14 years were studied for their hepatic functions.all cases were grouped into DF,DHF,DSS according to WHO criteria.The SGOT levels were elevated in 93%,SGPT elevation seen in 78 %.Hepatic dysfunction was observed more in DHF and DSS group compared to DF group. About 17.27 % had >10 times increase in liver enzymes. No correlation was found between the degree of hepatic enlargement or hepatic tenderness with abnormal liver functions.

Aidil Ario Darmawan et al conducted a study titled "Liver function tests of patients with dengue fever ,dengue hemorrhagic fever and dengue shock syndrome in tropic and infectious disease ward in the department of internal medicine , Dr. Soetomo Hospital ,Surabaya"[132]The study was a descriptive study where the data were collected from medical records of patients with dengue fever , Dengue Hemorrhagic fever and Dengue Shock Syndrome from august 1st 2010 to may 31st 2011 in the department of internal medicine, RSUD Dr.Soetomo,Surabaya.162 medical records

were qualified for the research. The mean values of AST and ALT was higher in patients with Dengue hemorrhagic fever than in patients with Dengue fever. However the mean values of AST and ALT in patients with Dengue Shock Syndrome was not in the highest range.

Kaur Ramandeep et al conducted a study titled “Haematological and biochemical changes in Dengue fever.” [133]The study was conducted in Gamma Diagnostic Laboratory ,Moga. A Case control study was done in Gamma Diagnostic centre Moga,20 individuals each were taken in the healthy control group (Group A) and Dengue patients (Group B) . CBC and liver enzyme levels were compared among the two groups. SGOT and SGPT values are raised in Dengue patients as compared to healthy controls with SGOT range between 74 -420 IU/L among the dengue patients and 8-40 IU/L among the healthy group. The values of SGPT range from 12-30 IU/L in healthy controls and 53-390 IU/L in dengue patients

METHODOLOGY

STUDY DESIGN:

Prospective Cohort Study

STUDY PLACE:

The Department of Paediatrics, Government Coimbatore Medical College and Hospital.

STUDY PERIOD:

1 year from July 2016 to June 2017

STUDY POPULATION:

All patients from 1 month to 12 years admitted in pediatric department and satisfying the inclusion criteria.

INCLUSION CRITERIA

All patients from 1 month to 12 years admitted with fever and thrombocytopenia.

EXCLUSION CRITERIA

Chronic Liver Disease

SAMPLE SIZE

Calculation formula

$$n = \frac{t^2 \times p\,(1 - p)}{m^2}$$

Description :

n = required sample size

t = confidence level of 95%

(standard value of 1.96)

p = Expected Frequency of the Factor under study- 14.5%

(standard value of 0.05)

m= margin of errorof 5 %

(standard value of 0.05)

$$n = \frac{1.96^2 \times 0.145(1 - 0.145)}{.05^2} = 190$$

Contingency

The sample is further increased by 5 % to account for contingencies such as non response or recording error.

n + 5 % = 162 + 5 % = 200 samples

Sample Size Calculated = 200

SAMPLING TECHNIQUE: Purposive sampling

DROPOUTS: Nil

MANEUVER

The study was undertaken in the department of Paediatrics, Govt Coimbatore medical college and hospital, during the study period from July 2016 to July2017.

All paediatric patients admitted with fever and thrombocytopenia during the study period who were fulfilling the inclusion criteria, were registered for the study after informed consent and ethical committee approval. Detailed proforma was filled with, age, sex, address, presenting complaints, clinical features and examination findings. Lab investigations like CBC, SGOT, SGPT levels at the time of admission (from day2-6 of fever)were estimated. 1ml Blood is collected by venepuncture method and CBC is analysed using Sysmex XP-300 automated hematology analyser. SGOT and SGPT were determined by kinetic method. All the patients were followed up and IGM dengue test was done after 6 days of fever. Patients were closely monitored for features of Dengue haemorrhagic fever or Dengue shock syndrome. Final diagnosis at the time of discharge was done based on the IgM Dengue report (done after 6 days of fever) and the clinical course of the patient.

Data management and Statistical analysis

The data are reported as the mean +/- SD or the median, depending on their distribution. Frequencies are expressed in percentages. Comparsion between groups was made by the Non parameteric Mann - Whitney test. The chi square test and Fishers" exact test were used assess differences in categoric variables between groups. Binary Logistic regression was used to assess the variables & Odds ratio was performed. A p value of <0.05 using a two-tailed test was taken as being of significance for all statistical tests. All data were analyzed with a statistical software package (SPSS, version 16.0 for windows)

RESULTS & OBSERVATIONS

Table 5.1 AGE & Gender DISTRIBUTION OF STUDY GROUP

AGE	Male	Female	Number	Percentage
<1 year	9	5	14	7
1-5 years	20	28	48	24
6-12years	67	71	138	69
Total	96	104	200	100

Chart 5.1 : Age distribution of study group

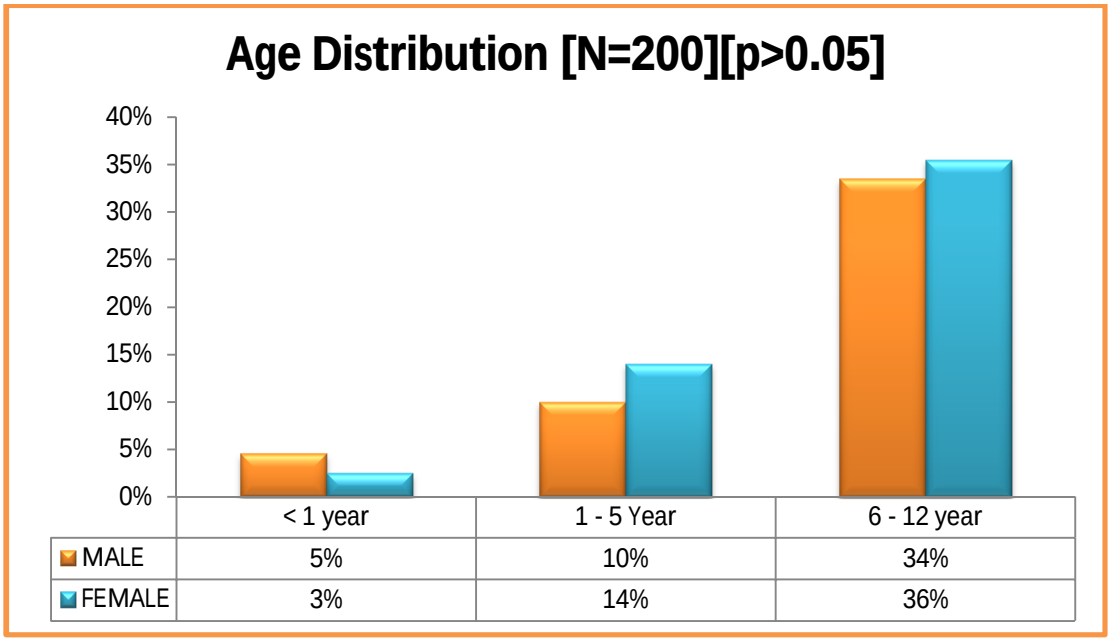
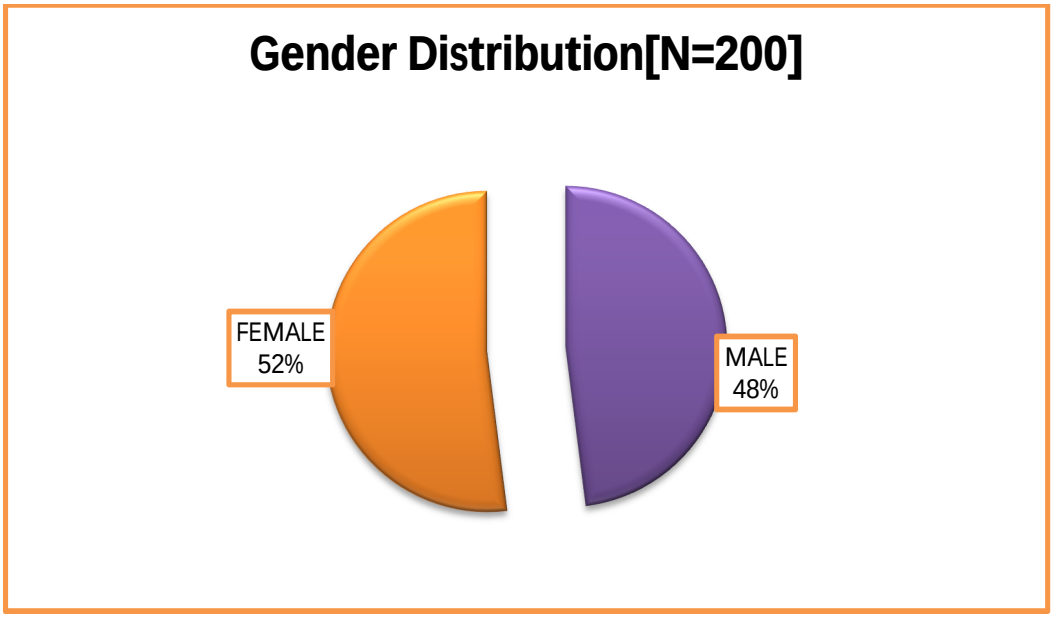


Chart 5.2: Gender distribution in study group

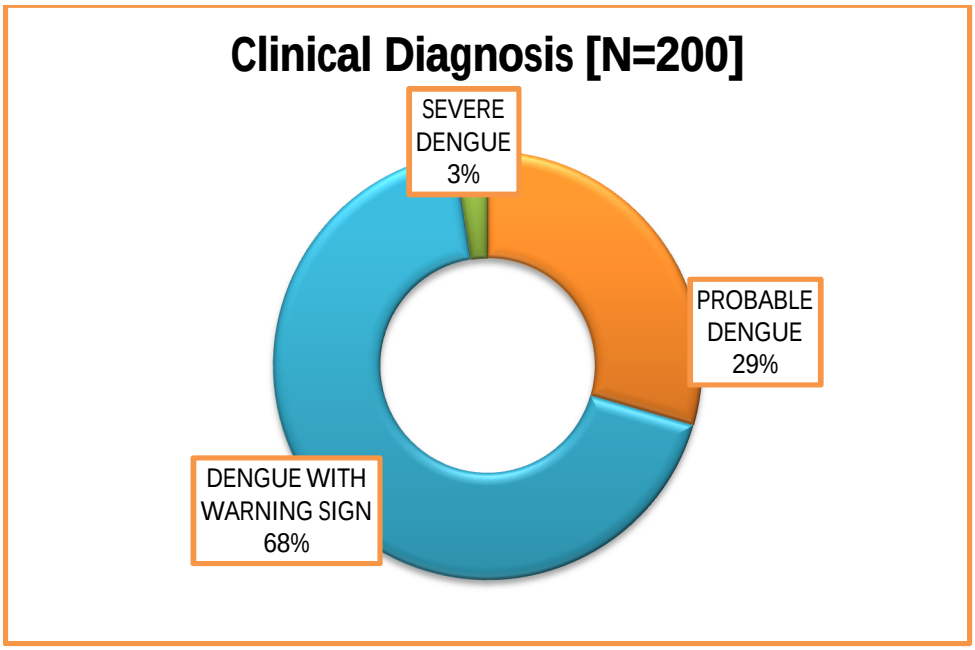


A total of 200 patients were included in the study. Of these 138 cases (69%) belonged to 6-12 years age group , 48 cases (24%) belonged to 1-5 years age group and 14 cases (7%)were infants, which showed that most of the study population was in the age group of 6-12 years.96 cases (48%) were males and 104 cases (52%) were females, with a slight female predominance.

Table 5.2 Clinical diagnosis at admission

Clinical diagnosis	Number	Percentage
Probable Dengue	59	30
Dengue fever with warning signs	136	68
Severe Dengue fever	5	3

Chart 5.3 Clinical Diagnosis at the time of Admission

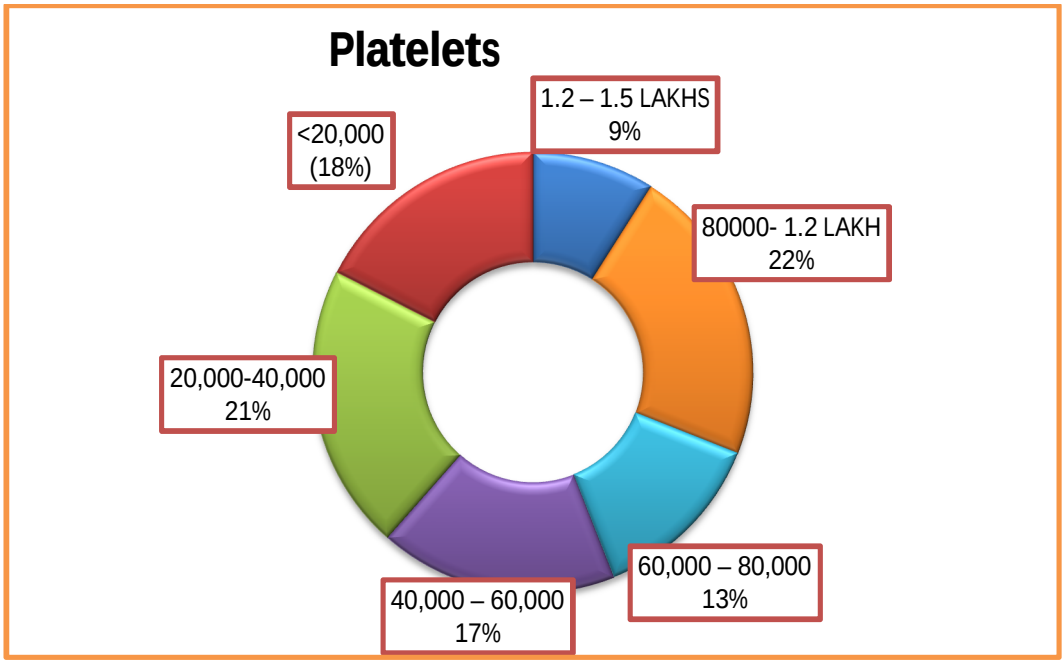


At the time of admission based upon the clinical features and examination, 59 cases (29%) were classified under Probable Dengue ,136 cases (68%) as Dengue fever with warning signs and 5cases(3%) as Severe dengue presenting with shock at the time of admission. 68% of the children presented with thrombocytopenia and warning signs. The most common warning sign being abdominal pain and abdominal tenderness.

Table 5.3 Thrombocytopenia Levels in study group

Platelets	Number	Percentage
1.2 -1.5 Lakhs	**18**	**9**
80,000-1.2 Lakhs	**44**	**22**
60,000- 80,000	**26**	**13**
40,000-60,000	**35**	**18**
20,000-40,000	**42**	**21**
<20,000	**35**	**18**

Chart 5.4 Thrombocytopenia Levels in study group



Thrombocytopenia was divided into 6 groups. Out of the 200 cases 62(31%) had only mild thrombocytopenia of 80,000-1.5 lakhs. 35 cases (18%) had very severe thrombocytopenia of less than 20,000.103 cases(52%)had platelet count between 20,000 and 80,000.

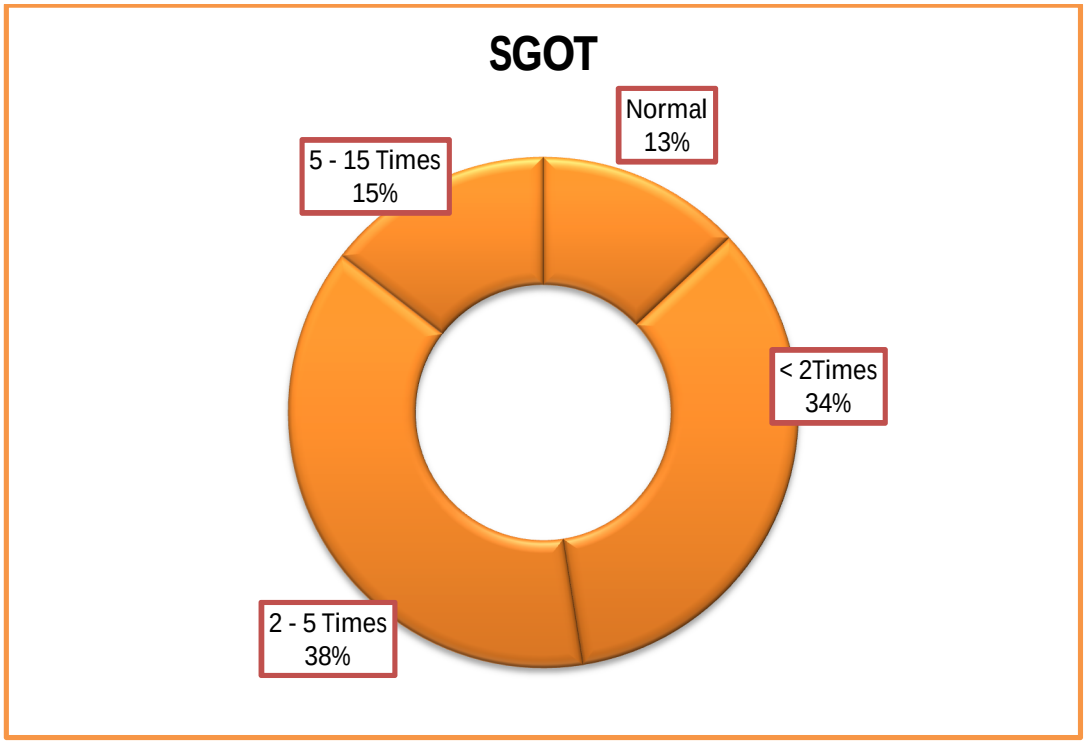
Table 5.4 Reference values of liver enzymes

Upper limit	SGOT U/L	SGPT U/L
1 month -1year	**22-63**	**12-45**
1-2years	**20-60**	**5-45**
3-9 years	**15-50**	**5-45**
10-12 years	**10-40**	**5-45**

Table 5.5 SGOT levels in study group

SGOT	Number	Percentage
normal	26	13
<2 times	69	35
2-5times	76	38
5-15 times	29	15

Chart 5.5 SGOT Elevation in study group

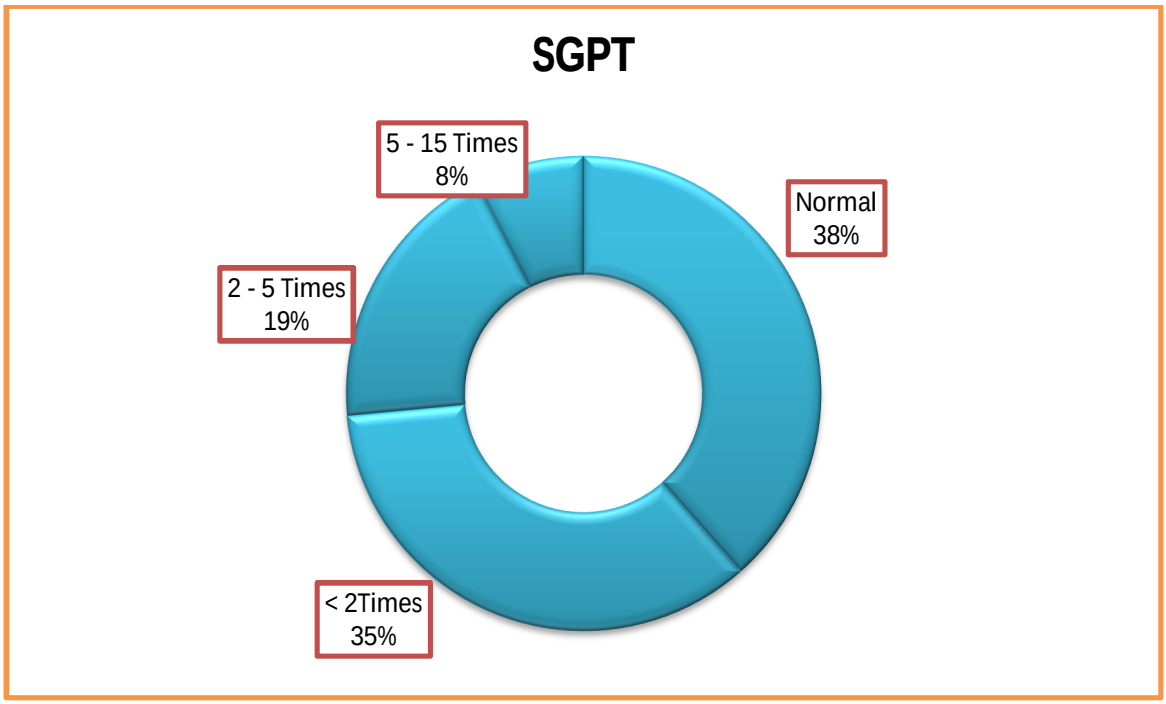


13%(26 cases) of the children with fever thrombocytopenia had normal SGOT levels.34 % (69 cases)had a mild elevation of <2 times the normal level.38%(76 cases) had high enzyme elevation of 2-5 times.15 % (29 cases)had very severe elevations of >5 times.

Table 5.6 SGPT in study group

SGPT	Number	Percentage
Normal	77	38
<2 times	70	35
2-5times	38	19
5-15times	15	8

Chart 5.6 SGPT Elevation in study group

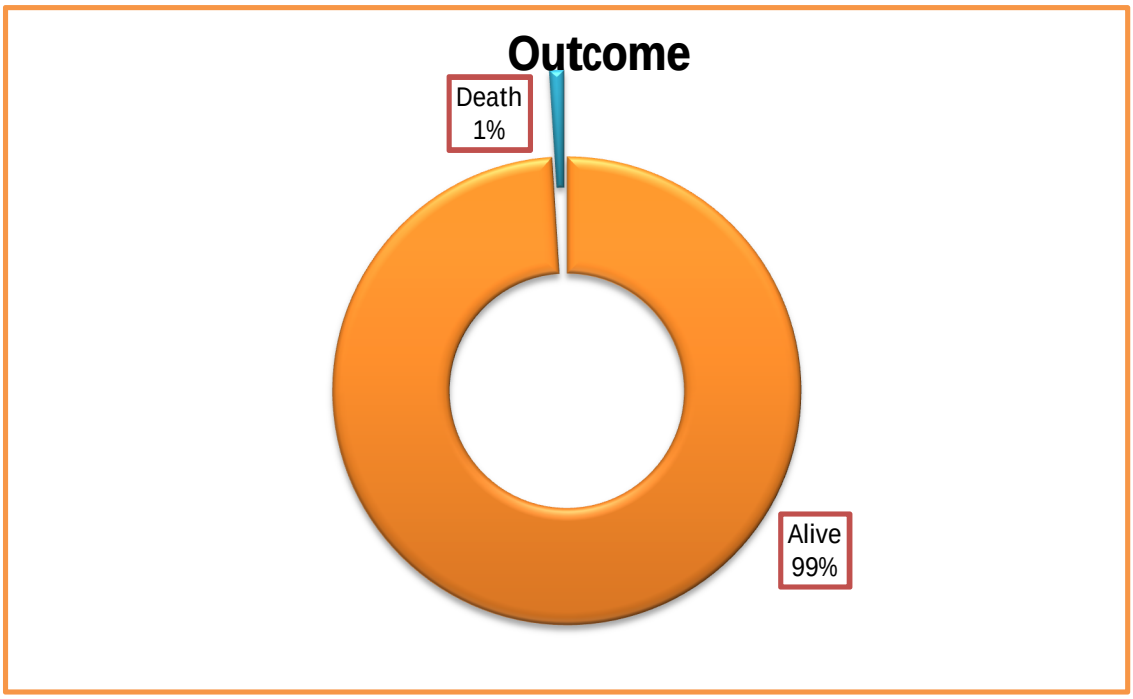


Unlike SGOT 38% (77 cases)of the children in our study had normal SGPT levels .35 %(70 cases) had mild elevation(<2 times) . 19%(38cases) had high elevations of 2-5 times.8 %(15cases)had very severe elevation of >5 times.

Table 5.7 Outcome

Outcome	Number	Percentage
Alive	198	26
Death	2	29

Chart5.7Outcome

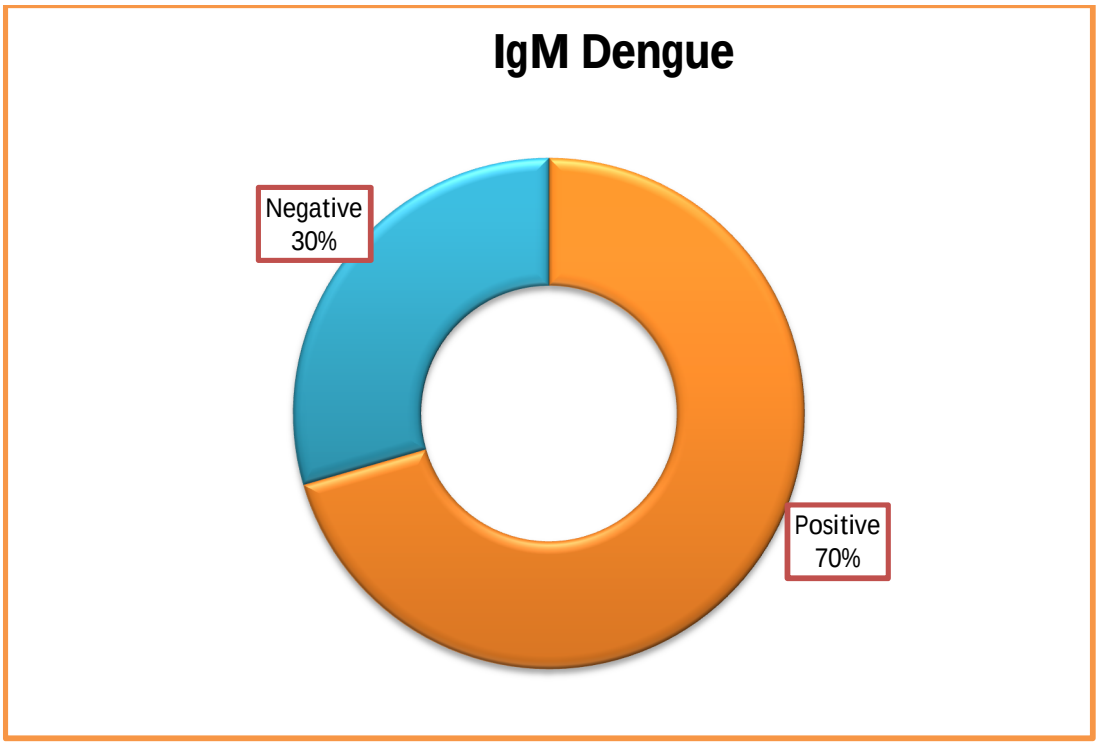


Out of the 200 children included in the study there are only 2 deaths. Mortality rate is being only 1%. Out of the 2 deaths, one case was IgM Dengue positive and the other was IgM Dengue negative. All survivors recovered completely. None had sequelae or chronic liver disease.

Table 5.8 IgM Dengue Results

	Number	percentage
IgM Positive	141	70
IgM Negative	59	30

Chart 5.8 IgM Dengue Results

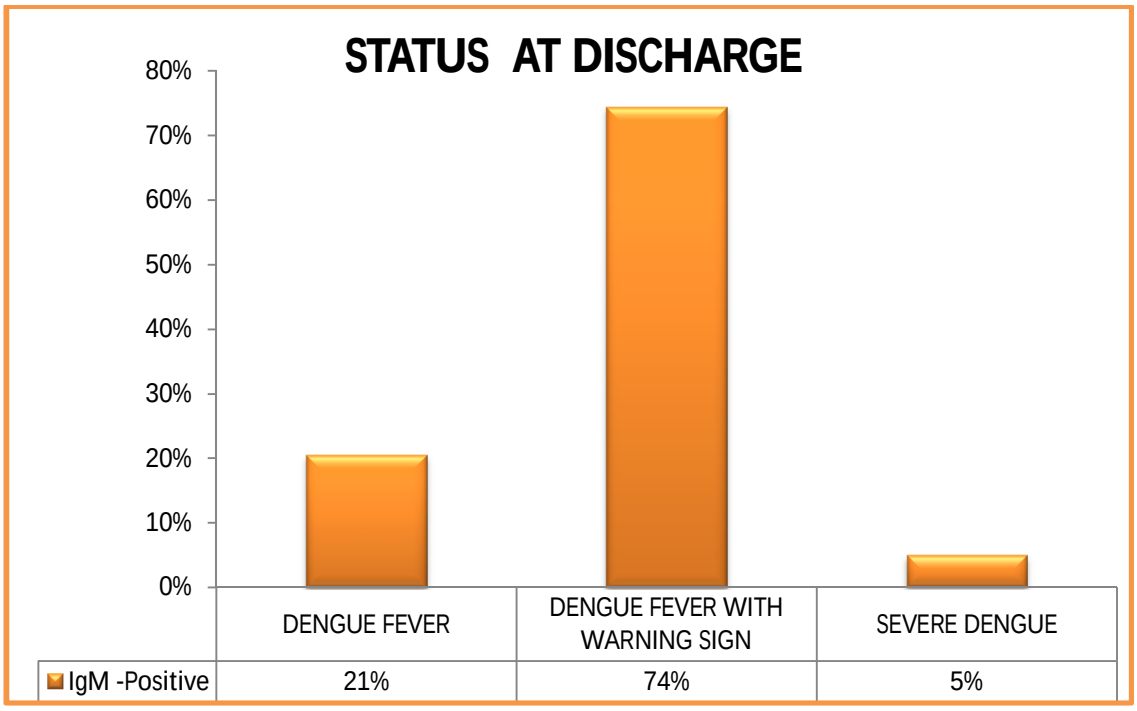


Out of the 200 study subjects final IgM Dengue ELISA test showed 70 % (141 cases) to be IGM Positive and 30 % (59 cases) to be IGM Negative. As per the WHO guidelines only IgM dengue positive cases were taken as Dengue fever. NS1 Ag positivity alone or IgG Dengue positive alone or IgM Dengue equivocal results were not considered in the final diagnosis as Dengue.

Table 5.9 Status at discharge

Status at discharge	IgM Dengue Positive	IgM Dengue Negative	Total	Percentage
Dengue fever	29	0	29	15
Dengue fever with warning sign	105	0	105	53
Severe dengue	7	0	7	4
Others	0	59	59	30
Total	141	59	200	200

Chart 5.9 Status at discharge



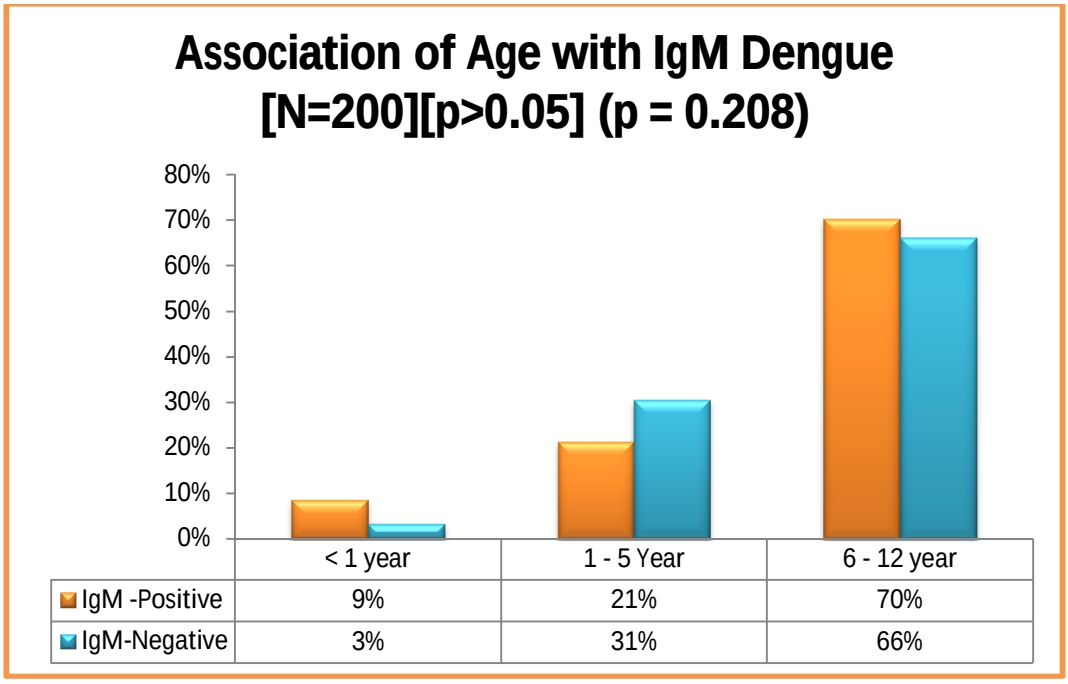
At the time of discharge based on the clinical severity and IgM Dengue results,105 cases (53%) had a final diagnosis of Dengue fever with warning signs,29 cases (15%) were diagnosed to have Dengue fever,7 cases (4%) were diagnosed to have Severe Dengue fever and 59 cases (30%) with IgM Dengue negative results had diagnosis other than Dengue fever.

Children with severe Dengue fever went in for many complications like myocarditis, pulmonary oedema/ fluid overload, acute encephalopathy syndrome, acute kidney injury, pneumonia and sepsis.

Table 5.10 Association of Age with IgM Dengue

Age	IgM Dengue Positive	IgM Dengue Negative	Total
1month- 1 year	12	2	14
1 - 5 Year	30	18	48
6 - 12 year	99	39	138
Total	141	59	200

Chart 5.10 Association of Age with IgM Dengue

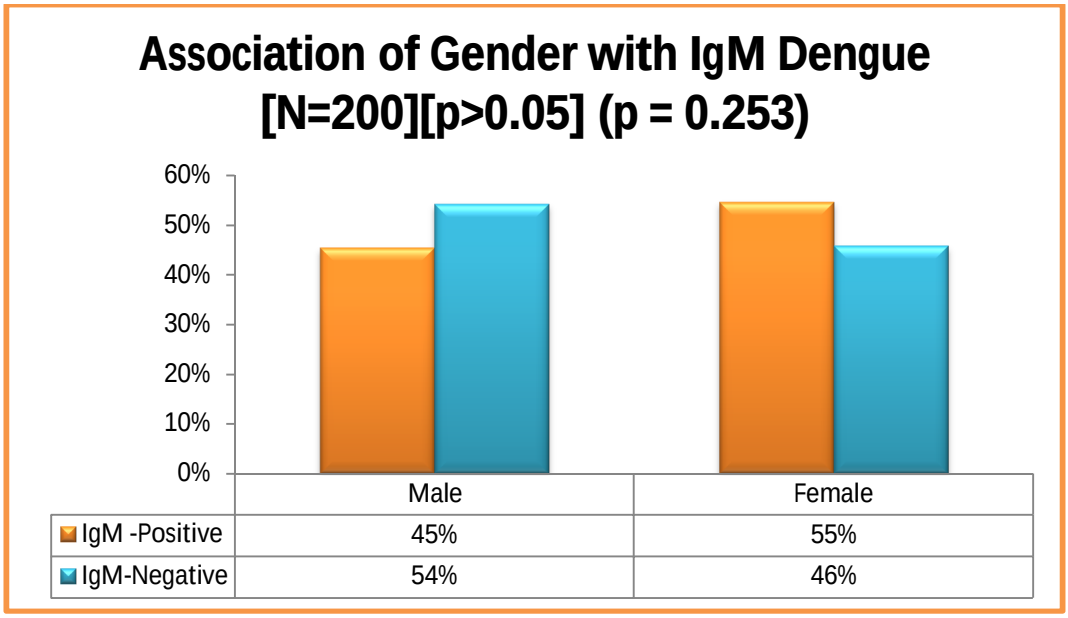


No significant association was found between the age group and the IgM dengue positivity.

Table 5.11 Association of Gender with IgM Dengue

Gender	IgM		Total
	Positive	Negative	
Male	64	32	96
Female	77	27	104
Total	141	59	200

Chart 5.11 Association of gender with IgM Dengue

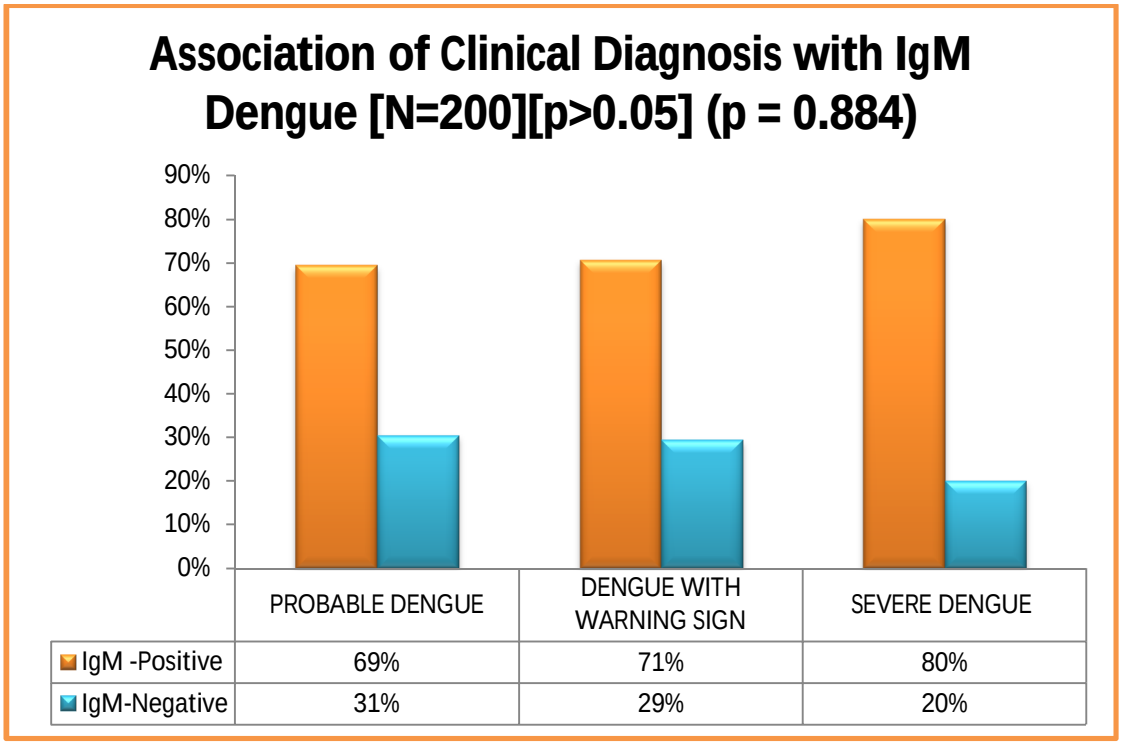


No significant association was found between gender and IgM dengue positivity.

Table 5.12Association of clinical diagnosis with IgM Dengue positivity

Clinical diagnosis	IgM Dengue positive	IgM Dengue negative
Probable Dengue	41	18
Dengue with warning signs	96	40
Severe Dengue	4	1

Chart 5.12 Association of clinical diagnosis with IgM Dengue positivity

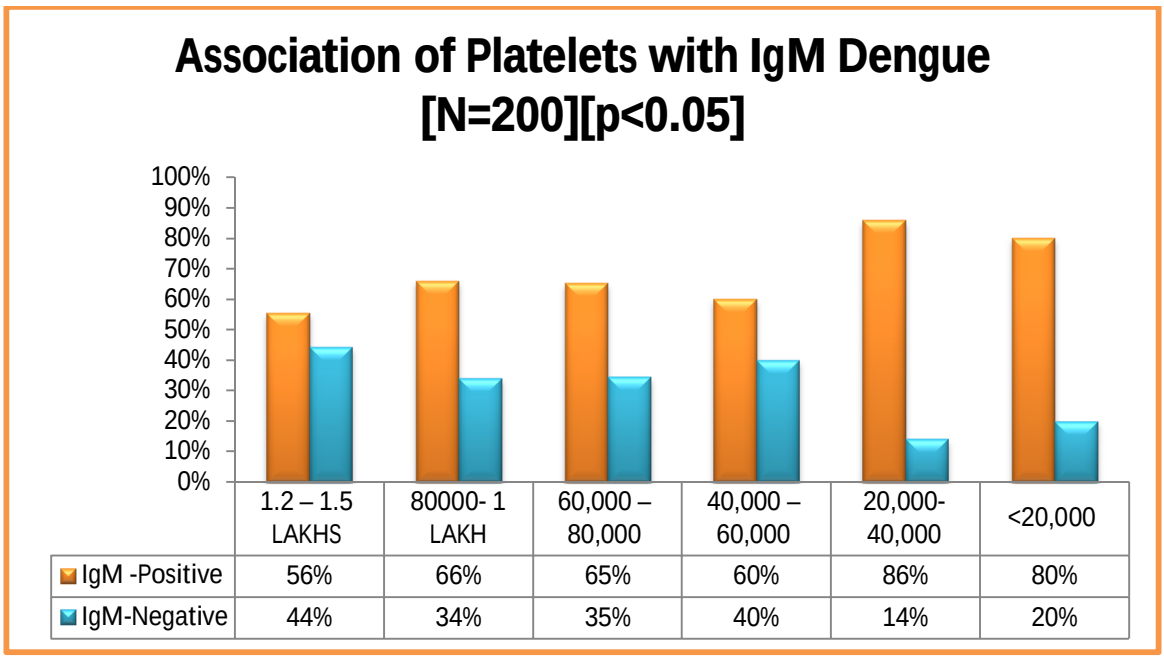


No statistically significant correlation was found between clinical diagnosis at the time of admission and IgM Dengue positivity test done later.

Table 5.13Associationof thrombocytopenia with IgM Dengue positivity

PLATELETS	IgM Dengue positive	IgM Dengue negative
1.2 – 1.5 Lakhs	10	8
80,000 – 1.2 Lakhs	29	15
60,000 – 80,000	17	9
40,000 – 60,000	21	14
20,000-40,000	36	6
<20,000	28	7

Chart 5.13 Association of thrombocytopenia with IgM Dengue positivity



There was a significant statistical correlation between the severity of thrombocytopenia and IgM Dengue positivity with a p value of<0.05.

Chart 5.14 No of IgM Dengue positive cases and platelet count

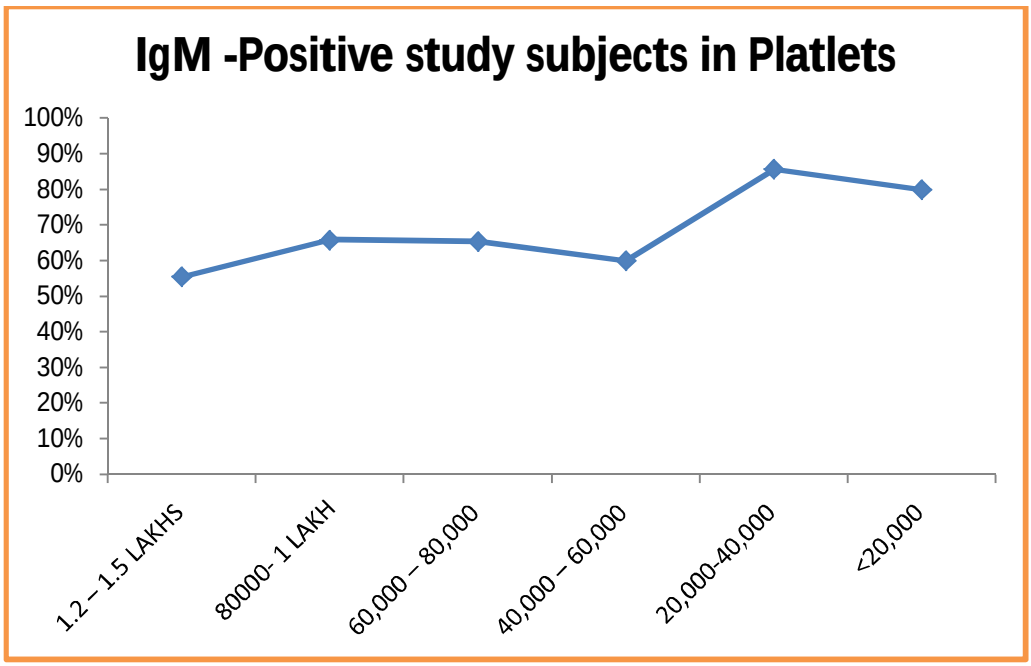
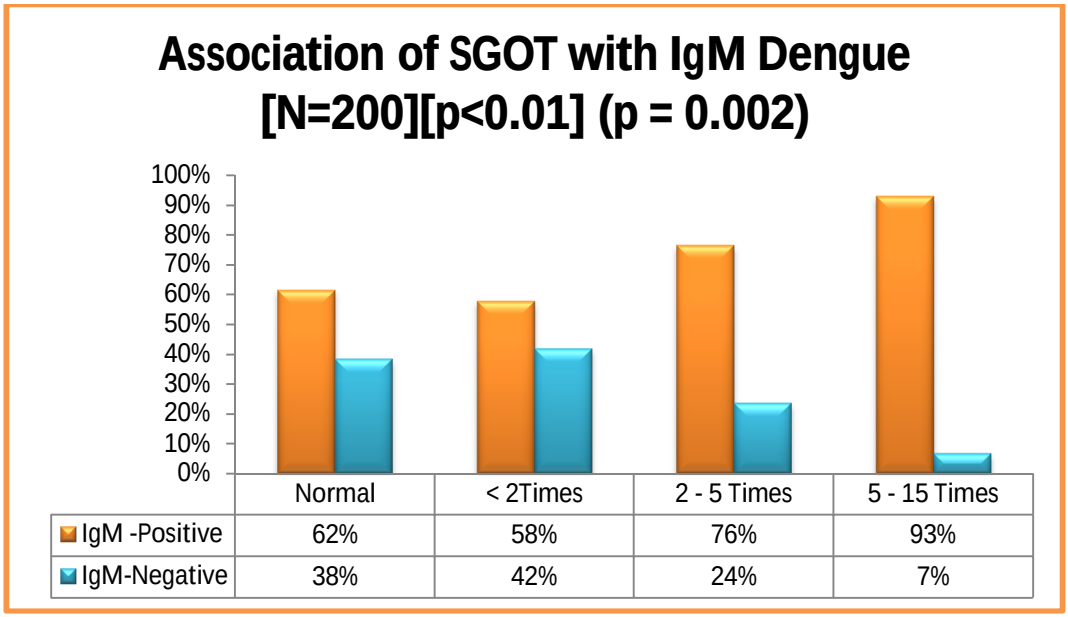


Chart showing increase in IgM positivity with progressive thrombocytopenia.

Table 5.14Association OF SGOT level with IgM Dengue positivity

SGOT	IgM positive	IgM negative
Normal	16	10
<2 times	40	29
2-5 times	58	18
5-15times	27	2

Chart5.15 Association of SGOT levels with IGM positivity

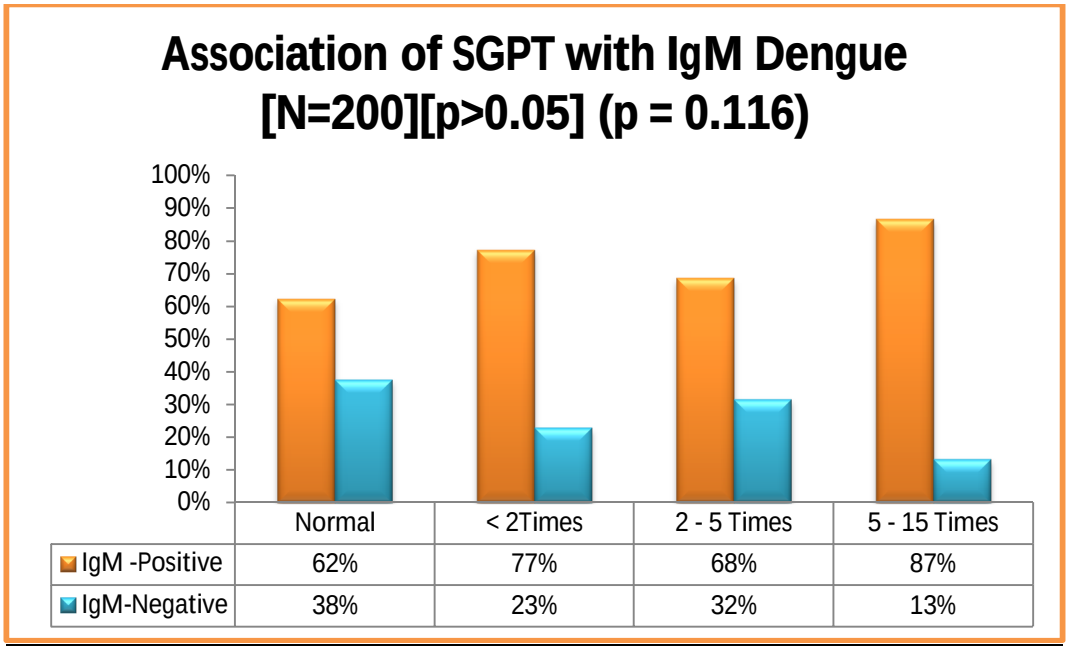


A significant association was found between degree of elevation of SGOT with IgM dengue positivity with a p value of <0.01.

Table 5.15 Association OF SGPT with IgM Dengue positivity

SGPT	IgM Dengue positive	IgM Dengue negative
Normal	48	29
<2 times	54	16
2-5 times	26	12
5-15 times	13	2

Chart 5.16 Association of SGPT with IGM positivity

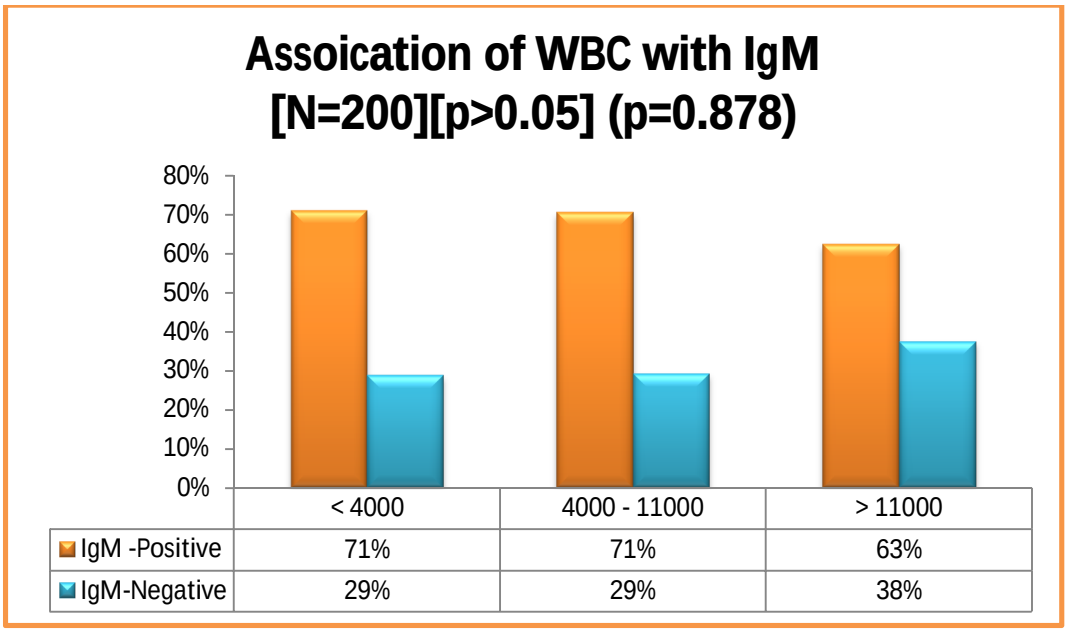


No association was found between SGPT levels and IgM dengue positivity.

Table 5.16 Association of WBC counts with IgM Dengue positivity

WBC	Positive	Negative
<4000	59	24
4000-11,000	77	32
>11,000	5	3

CHART 5.17 Association of WBC counts with IgM Dengue positivity

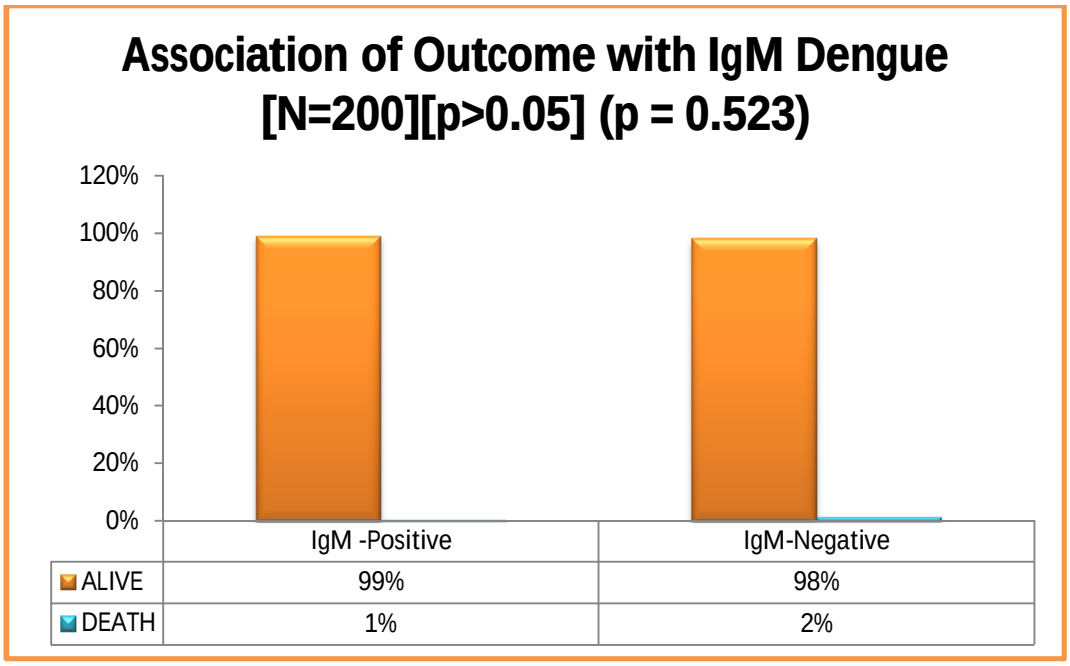


WBC counts in the study group were studied.83cases had leucopenia (<4000), 109 cases had normal WBC counts (4000-11,000),8 cases had leucocytosis. No correlation was found between leucopenia and Ig M Dengue positivity.

Table 5.17 Association of Outcome with IgM Dengue

Outcome	IgM dengue positive	IgM dengue negative	Total
alive	140	58	198
death	1	1	2

Chart 5.18 Association of Outcome with IgM Dengue

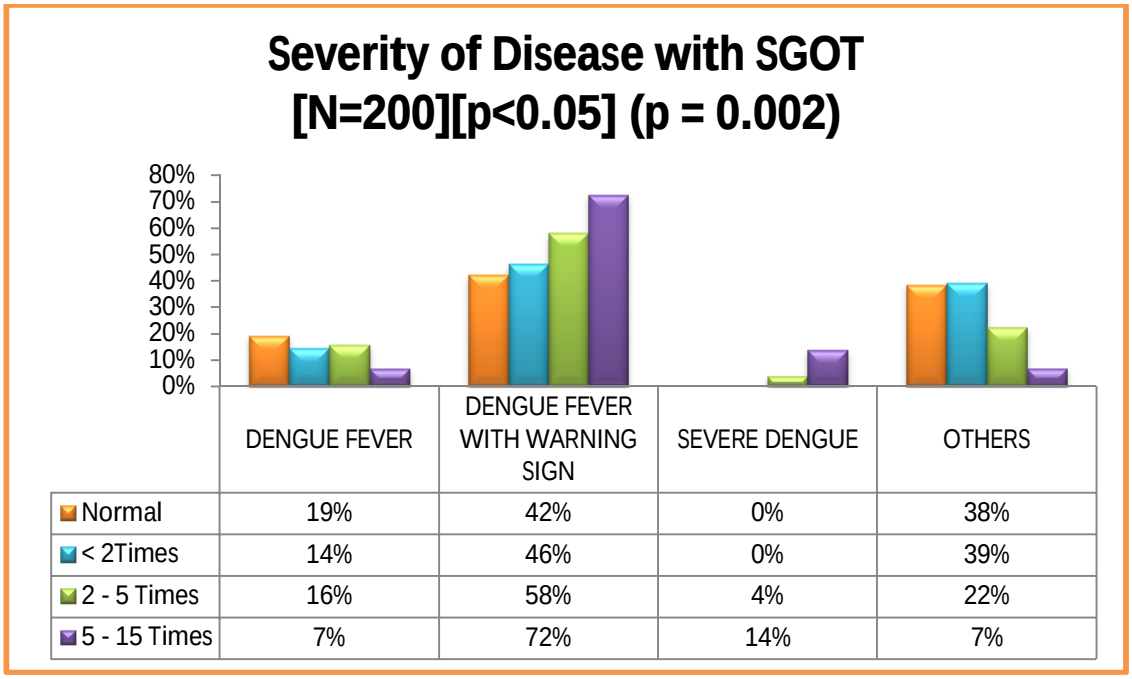


The mortality rate in the study population was 1 %.

TABLE 5.18 Association of SGOT with Severity of Dengue

Severity of Disease					
SGOT	**Dengue fever**	**Dengue fever with warning sign**	**Severe dengue**	**Others**	**Total**
Normal	5	11	**0**	10	26
< 2Times	10	32	**0**	27	69
2 - 5 Times	12	44	3	17	76
5 - 15 Times	2	21	4	2	29
Total	29	108	7	56	200

CHART 5.19 Association of SGOT with Severity of Disease

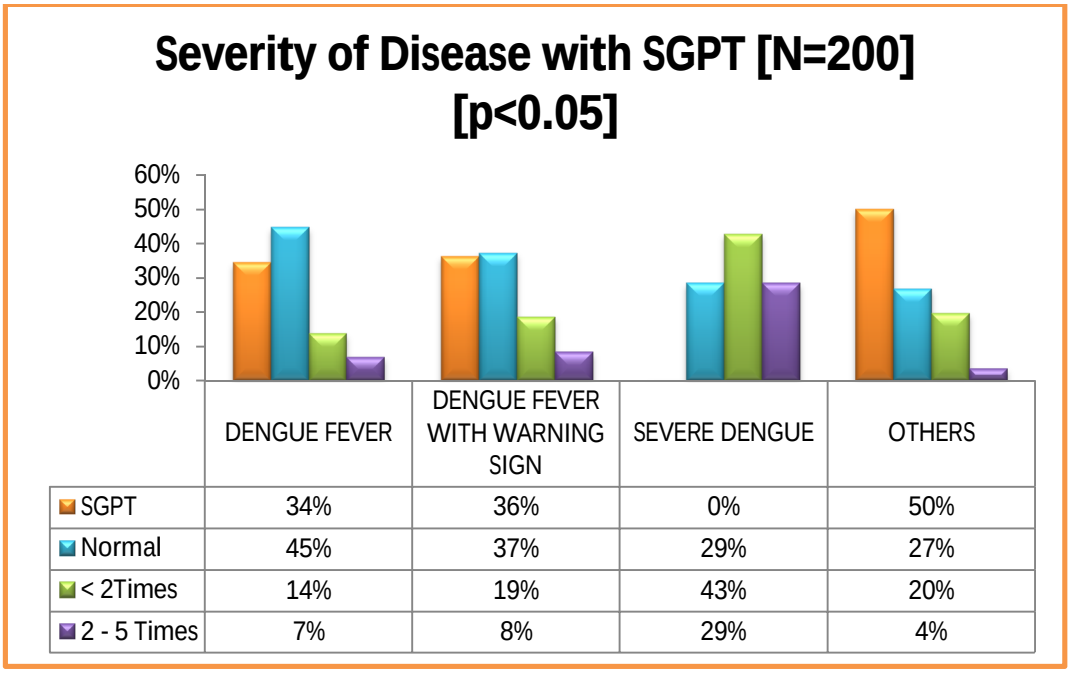


None of the cases with severe Dengue had normal SGOT levels. Hence normal SGOT level has a very good negative predictive value. (P=0.002). In Dengue fever with warning signs 90% had elevated liver enzymes and only 10%had normal SGOT levels. In Dengue fever patients 83% had elevation of liver enzymes and 17% had normal SGOT levels. In non-dengue fever patients 18% had normal SGOT and 82% had elevated SGOT levels. There is a linear correlation between degree of elevation of SGOT with severity of illness (elevation of SGOT >5 times than the normal seen in 3.5% of non-dengue, in 6% of dengue fever, in 19% of dengue with warning sign, in 60% of severe dengue cases and this difference is statistically significant: $p<0.001$)

TABLE 5.18 Association of SGPT with Severity of Dengue

Severity of Dengue					
SGPT	**Dengue fever**	**Dengue fever with warning sign**	**Severe dengue**	**Others**	**Total**
Normal	10	39	0	28	77
< 2Times	13	40	2	15	70
2 - 5 Times	4	20	3	11	38
5 - 15 Times	2	9	2	2	15
Total	29	108	7	56	200

CHART 5.20 Association of SGPT with severity of dengue

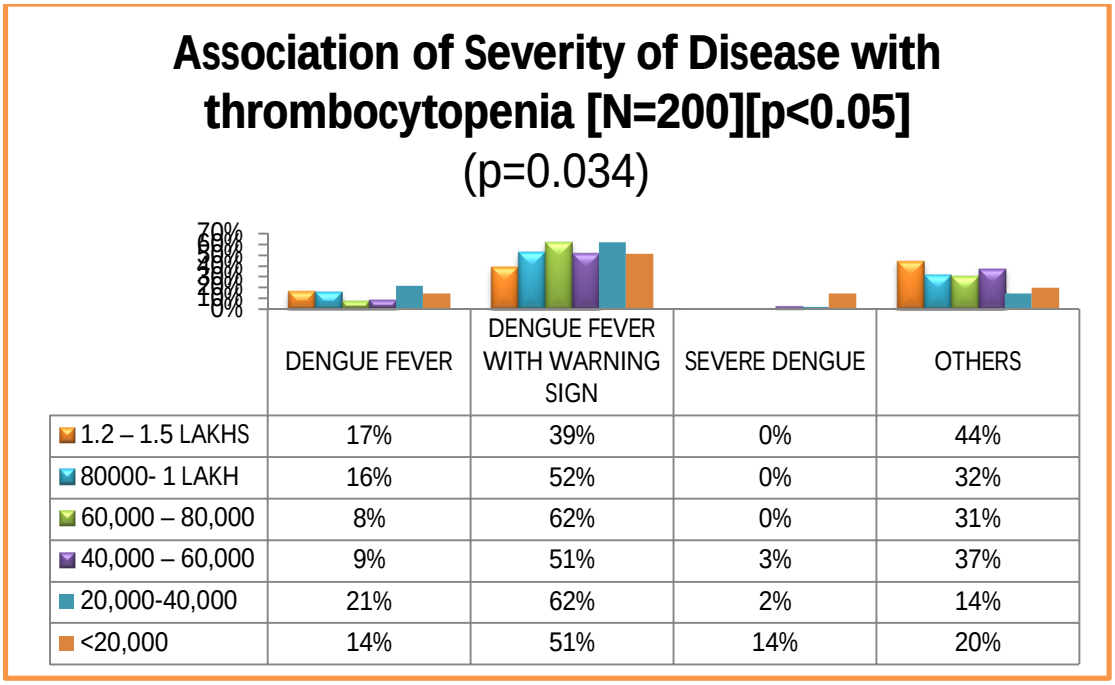


All cases of severe Dengue had elevated SGPT levels. Hence normal SGPT levels has got a good negative predictive value . In dengue fever cases 35 % had normal SGPT levels and 65% had elevated SGPT levels.In dengue fever with warning signs 36%had normal SGPT levels and 64% had elevated SGPT levels whereas in non-dengue fever cases 50% had normal SGPT levels and 50% had elevated SGPT levels. Hence elevated SGPT levels in the first week of illness is associated with severe illness with a linear correlation between degree of elevation of liver enzymes with severity of disease (Elevation of SGPT >5 times than the normal seen in 3.5% of non-dengue, in 6% of dengue fever, in 8.3% of dengue with warning sign, in 29% of severe dengue cases and this difference is statistically significant: $p<0.05$.)

TABLE 5.20Association of thrombocytopenia with severity of dengue

Severity of Dengue					
Platelets	**Dengue fever**	**Dengue fever with warning sign**	**Severe dengue**	**Others**	**Total**
1.2 – 1.5 lakhs	3	7	0	8	18
80000- 1 lakh	7	23	0	14	44
60,000 –80,000	2	16	0	8	26
40,000 –60,000	3	18	1	13	35
20,000-40,000	9	26	1	6	42
<20,000	5	18	5	7	35
Total	29	108	7	56	200

CHART5.21 Association of thrombocytopenia with severity of disease

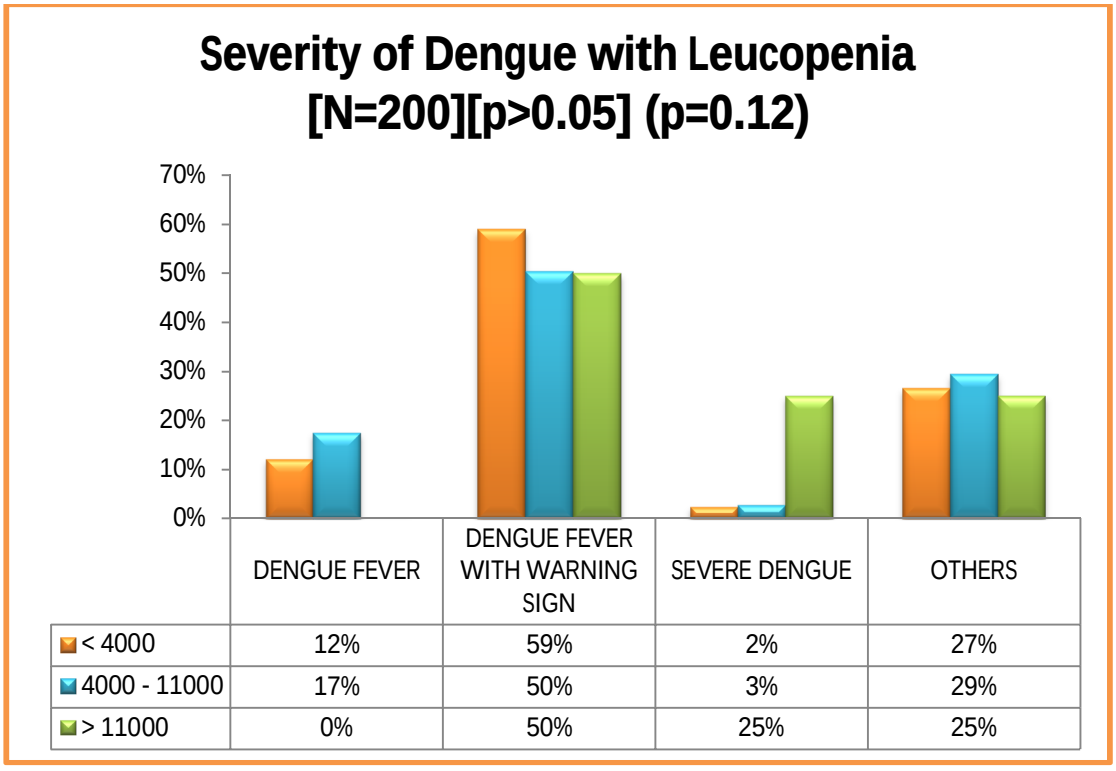


There is association between severity of thrombocytopenia with severity of illness with statistical significance (p value <0.05). Platelet counts <60,000 was associated with severe dengue.

Table 5.21Association of WBC with Severity of Disease

WBC	Dengue fever	Dengue fever with warning sign	Severe Dengue	Others
<4000	10	49	2	22
4000-11000	19	55	3	32
>11000	0	4	2	2

Chart 5.22 Association of WBC with Severity of Dengue



No correlation was found between leucopenia and severity of disease.

DISCUSSION

In this study among the total cases of 200 suspected VHF/dengue patients, presenting with fever > 2days with thrombocytopenia<1.5 lakhs, 141 Cases were dengue positive and 59 cases were non dengue.

Majority of children in this study group were in the 6-12 years age group. No statistically significant correlation was found between age and gender distribution in study population. No significant correlation found between age or gender distribution with IgM Dengue positivity or with severity of Dengue.

Platelet count of 1,50,000 was taken as cut off for thrombocytopenia. The severity of thrombocytopenia was assessed among the study group. Thrombocytopenia was sub classified into 6 groups. 35 cases (18%) had very severe thrombocytopenia of <20,000, 42 cases (21%)had platelet count between 20,000 – 40,000, 35 cases (18%) had platelet count between 40,000 to 60,000 , 26 cases (13%) had platelet count between 60,000 -80,000 , 44 cases (22%) had platelet counts between 80,000-1,20,000 and 18 cases (9%) had platelet counts above 1,20,000. This shows that majority (31%) had only mild thrombocytopenia of 80,000 – 1,50,000.

Association of severity of thrombocytopenia and IGM Dengue positivity was also studied. A statistically significant correlation was found between severity of thrombocytopenia with IgM Dengue Positivity, with a p value of

<0.05. Moreover a significant association was found between severity of thrombocytopenia with severity of illness. A platelet count of 60,000 and below was associated with severe dengue fever with a p value of <0.034.

SGOT levels were measured at the time of admission and followed up till complete recovery. 26 patients (13%) had normal SGOT levels, 69 patients (35%) had <2 times elevation, 76 patients (38%) had SGOT elevation of 2-5 times and 29 patients (15%) had very severe elevation of 5-15 times. This shows that most of the children suspected with VHF/dengue fever showed an elevation in SGOT levels (87%). This finding is similar to the results of studies conducted by **Vaibhav Shukla et al, Jagadishkumar K et al** and **Kaur Ramdeep et al.**

An SGOT enzyme elevation of 5-15 times was associated with 93 % IGM Dengue positivity and 2-5 times elevation was associated with 76% IgM Dengue positivity. Significant association was found between SGOT enzyme elevation and IgM Dengue positivity, with a p value of <0.01.study results similar to study conducted by **Kaur Ramandeep et al**. A linear correlation was found between severity of disease and degree of elevation of SGOT, with a significant p value of <0.05.

SGPT levels were normal in majority (39%) of the study subjects and < 2 times elevated in 70 cases (35%). In 38 cases (19%) SGPT showed elevations of 2-5 times and in 15 cases (8%) very high elevations of 5-15 times

were seen. This is consistent with the studies published by **Vaibhav Shukla et al**, **Kaur Ramandeep et al** and **Jagadishkumar K et al**.

No significant association was found between Severity of SGPT elevation and IGM Dengue positivity. But significant association was found between the degree of elevation of SGPT with severity of illness, with a p value <0.05.

Many studies like that of **Jagadishkumar K et al** and **Vaibhav Shukla et al** showed the same pattern of greater degree of SGOT elevation than SGPT elevation in Dengue patients. This because SGOT is a non-specific marker of liver injury hence it is also elevated in myocardial and in muscular injuries. But SGPT is elevated only in hepatic injury so less cases had SGPT elevation.

Outcome: 2(1%) out of 200 study subjects died. The mortality rate in the study population was only 1%.Being a tertiary care centre with high quality of care and protocol based management (as per WHO 2009 guidelines), has helped us to curtail the mortality rate to 1 %.Since the study has been done in a referral population the mortality rate in the community would be probably still lower than in our study.

There was no significant association between Clinical Diagnosis at the time of admission and the final diagnosis made at the time of discharge after obtaining IgM Dengue results, with a p value >0.05.

Association of WBC counts with IGM Positivity was studied. No significant association was found between leucopenia and IGM Dengue positivity. No significant association has been found between Leucopenia and severity of dengue in this study.

Association between outcome and IgM Dengue positivity was studied. No significant association was found between Outcome and IgM Dengue positivity, with a p value of >0.05.

SUMMARY

- Out of the 200 children included in the study, Most common age group in the study population was found to be 6 – 12 yrs and 96 were males and 104 were females.
- Abdominal pain and abdominal tenderness which are warning signs were found to be common presentation among the study group. Hence Dengue fever with warning signs constituted 68 % of the study population.
- 141 (70%) of the 200 children were IgM Dengue positive.
- 198 out of the 200 children survived. Being a tertiary care centre with high quality of care and protocol based management as per WHO 2009 guidelines the mortality rate was low, only 1 %. This correlates with the South East Asian studies which also showed a similar mortality rate of < 1 %.
- Study population were divided into 6 groups based upon the degree of thrombocytopenia.31 % had only mild thrombocytopenia of 80,000 to 1,50,000.
- A positive correlation was found between severity of thrombocytopenia and severity of disease, with a significant p value of<0.05.

- Significant association was found between the degree of elevation of SGOT and IgM Dengue positivity.

- Moreover a linear correlation was found between degree of elevation of SGOT with the severity of illness. Normal SGOT levels were found to have high negative predictive value.

- Hence elevation of SGOT liver enzyme can be used as an early predictor for severity of the disease.

- Significant association was found between elevated SGPT levels and severe Dengue .A linear correlation was found between severity of SGPT elevation with severity of illness. Hence elevated SGPT levels can be used to predict severity of illness.

CONCLUSION

Abdominal pain and abdominal tenderness are the common presentations in Dengue fever with warning sign and Severe Dengue and these symptoms should not be ignored in any febrile child. Elevated SGOT level were found in majority of study population and is found to have significant association with IgM Dengue positivity. Moreover severe elevation of SGOT level more than 5 times was associated with severe forms of dengue fever like Dengue Shock syndrome. Hence elevated SGOT levels during the first week of admission can be reliably used as an early predictor of Severe Dengue fever. Degree of elevation of SGOT levels can be used to predict the severity of dengue. Degree of elevation of SGPT was also found to have a significant linear correlation with the severity of dengue fever. Hence both elevated SGOT and SGPT level can be used as an early predictor of Severe Dengue fever. Both normal SGOT level and SGPT level has got a very high negative predictive value.

LIMITATIONS OF THE STUDY

This study was conducted in a tertiary care centre where referral bias could not be avoided. Majority of dengue fever and undifferentiated fever (viral syndrome) getting treatment in OPD or self-limited illness goes unnoticed. We studied only symptomatic cases with a probability to progress to very severe illness. Hence the overall mortality would still be lower.

RECOMMENDATIONS

Evaluation of SGOT, SGPT levels at the time of admission and during the early part of the illness should be made an integral part of the patient workup- in all children admitted with fever thrombocytopenia, so that severe cases of dengue fever can be identified earlier. With better triage, monitoring and timely intervention using protocol based management as per WHO2009 dengue guidelines, we can bring down the mortality rate in severe dengue fever.

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PROFORMA

ELIGIBILITY FORM - DENGUE STUDY SERIAL NO:

NAME : SEX : UNIT :

IPNO:

AGE : TIME OF ADMISSION:

DOA: TEMP ON ADMISSION:

FEVER DURATION PRIOR ADMISSION :

WHO CASE DEFINITION 2009

FEVER LASTING 2-7 DAYS	NO	YES
CRITERIA		
1.NAUSEA/VOMITING	NO	YES
2. RASH	NO	YES
3.ACHES AND PAINS	NO	YES
4.TOURNIQUET TEST	NO	YES
5.LEUKOPENIA<5000	NO	YES
6.WARNING SIGNS		
*LETHARGY RESTLESSNESS	NO	YES
*MUCOSAL BLEEDS		
NOSE	NO	YES
GUMS	NO	YES

*PERSISTENT VOMITING	NO	YES
*ABDOMINAL PAIN/ TENDERNESS	NO	YES
*LIVER ENLARGEMENT > 2 cm	NO	YES
*CLINICAL THIRD SPACE ACCUMULATION		
ASCITES	NO	YES
PLEURAL EFFUSION	NO	YES
*INCREASED HCT AND/ OR RAPID DECREASE IN PLATELETS	NO	YES

CLINICAL DIAGNOSIS

- FEVER 2 -7 DAYS AND ATLEAST 2 POSITIVE CRITERIA:
  PROBABLE DENGUE

- DENGUE WITH WARNING SIGNS
- SEVERE DENGUE

OUTCOME

NOT ELIGIBLE:

ELIGIBLE BUT REFERRAL/ ABSCONDED:

ELIGIBLE :

CASE REPORT FORM

ADMISSION

DATE :

TIME :

AGE :

SEX:

ADDRESS:

HISTORY:

ENROLLMENT :

WARNING SIGNS ON THE DAY OF ADMISSION:

SEVERE DENGUE / DENGUE SHOCK ON DAY 1

INVESTIGATIONS DONE OUTSIDE

PRIVATE HOSPITAL	GOVERNMENT HOSPITAL
INTERVENTIONS DONE	INTERVENTIONS DONE

DATE										
DAY OF ILLNESS	**DAY1**	**DAY2**	**DAY3**	**DAY4**	**DAY5**	**DAY6**	**DAY7**	**DAY8**	**DAY9**	**DAY10**
Day of admission										
1.WarningSigns										
Lethargy / restlessness										
Mucosal bleed Nose Gums Git bleed Haematuria										
Persistent vomiting										
Liver enlargement >2cm										
Abdominal pain										
Abdominal tenderness										
Clinical fluid accumulation Facial oedema Pleural effusion Ascites										

DATE										
DAY OF ILLNESS	**DAY1**	**DAY2**	**DAY3**	**DAY4**	**DAY5**	**DAY6**	**DAY7**	**DAY8**	**DAY9**	**DAY10**
Day of adm										
2. Shock										
Compensated shock										
Hypotensive shock										
3.other complications Encephalitis Heart failure Ards Acuteliver failure Acute renal failure										
4.investigatios										
Total Count <4000										
>11000										
Differential count Neutrophils										
Lymphocytes										

DATE										
DAY OF ILLNESS	**DAY1**	**DAY2**	**DAY3**	**DAY4**	**DAY5**	**DAY6**	**DAY7**	**DAY8**	**DAY9**	**DAY10**
Day of adm										
2. Shock										
Compensated shock										
Hypotensive shock										
3.Other complications Encephalitis Heart failure Ards Acuteliver failure Acute renal failure										
4.Investigations										
Total Count <4000										
>11000										
Differential Count Neutrophils										
Lymphocytes										

DATE										
DAY OF ILLNESS	**DAY1**	**DAY2**	**DAY3**	**DAY4**	**DAY5**	**DAY6**	**DAY7**	**DAY8**	**DAY9**	**DAY10**
DAY OF ADM										
PLATELETS NORMAL										
1.2 -1.5 lakhs										
80,000 – 1 lakh										
60,000 -80,000										
40,000- 60,000										
20,000-40,000										
<20,000										
HAEMATOCRIT										
LFT										
AST										
NORMAL										
2-5 TIMES										
5-15 TIMES										
ALT										
ALP										
BILIRUBIN										
TOTAL PROTEIN										
ALBUMIN										
GLOBULIN										
PT- APTT										

DATE										
DAY OF ILLNESS	**DAY1**	**DAY2**	**DAY3**	**DAY4**	**DAY5**	**DAY6**	**DAY7**	**DAY8**	**DAY9**	**DAY10**
DAY OF ADM										
Ultrasound Abdomen										
Normal										
Abnormal Pleural effusion Hepatomegaly Ascites Others										
IgM DENGUE										
Assessment at Discharge										
Clinical outcome at Discharge Dengue fever Df with warning signs Severe Dengue										
Status at discharge Recovered Died Left AMA										
Haematocrit										
LFT										
AST										
NORMAL										
2-5 TIMES										
5-15 TIMES										
ALT										

ALP										
Bilirubin										
Total Protein										
Albumin										
Globulin										
PT- APTT										

CONSENT FORM

I have come to know that **Dr. VEENA SURENDRAN**, Postgraduate in the Departmentof Paediatrics is conducting a study on the topic,**"LIVER ENZYMES AS AN EARLY PREDICTOR OF COMPLICATED DENGUE FEVER"** I understand that my child will not have to suffer anyharmful consequences as a result of the study nor will I have any financial constraints.

It is understood that blood will be collected from my child for the purpose of conductingthis study.

I also understand that I can withdraw myself from this study at any point oftime and by doing so it will not affect the treatment in any manner. Understanding allthese, I wholeheartedly agree to take part in this study.

Signature

Name of the guardian:

Relation:

Place:

Date:

KEY TO MASTER CHART

Clinical Diagnosis

1 - Dengue Fever

2 - Dengue Fever with warning Sign

3 - Severe Dengue

4 - Other Diagnosis

SGOT

1 - Normal

2 - < 2 times

3 - 2-5 times

4 – 5-15 times

SGPT

1 - Normal

2 - < 2 times

3 - 2-5 times

4 - 5-15 times

WBC

1 - <4000

2 – 4,000-11,000

3 - >11,000

MASTER CHART

S.No	Name	Age	Sex	CLINICAL DIAGNOSIS	platelets	SGOT	SGPT	IgM Dengue	Outcome	Status at Discharge	WBC
1	MEINMOZHIYAN	1	1	2	7	4	3	1	1	2	1
2	DHARANI	2	2	2	3	1	1	1	1	2	2
3	ELAKIYA	3	2	2	7	3	2	1	1	2	3
4	RAMYA	3	2	2	6	3	1	1	1	2	3
5	MADHIVANAN	1	1	2	7	1	1	1	1	2	3
6	MADHESH KUMAR	3	1	1	6	4	3	1	1	2	1
7	SUJITHA	3	2	2	4	3	2	1	1	2	3
8	HEMANTH	3	1	2	5	4	4	2	1	4	3
9	SHANMATHY	3	2	2	7	4	4	1	1	2	1
10	KARTHIK	3	1	2	6	2	2	1	1	2	3
11	SARAVANAN	3	1	2	3	4	3	1	1	2	3
12	DHARANI	2	2	2	3	2	1	2	1	2	1
13	KEERTHANA	1	2	2	7	4	3	1	2	3	1
14	MUKILAN	1	1	1	7	3	2	1	1	3	3
15	SOUMYA	3	2	2	5	2	1	1	1	2	3
16	PAUL	3	1	2	3	2	1	2	1	4	1
17	SUBASREE	3	2	1	6	3	1	1	1	2	1
18	ROHINI	3	2	1	2	1	1	2	1	4	3

19	MAHALEKSHMI	3	2	2	7	1	1	2	1	4	1
20	GAYATHRI	3	2	2	5	1	1	2	1	4	3
21	AYSHA	2	2	2	7	3	3	1	1	3	3
22	BALAMURUGAN	3	1	2	6	3	2	1	1	1	3
23	JAGATH HARI	3	1	1	3	3	2	1	1	1	1
24	VIYAS	3	1	1	2	1	1	2	1	4	1
25	DIVESH	3	1	2	6	3	2	1	1	1	3
26	SRIDHAR	1	1	1	3	2	4	1	1	1	1
27	KRISHNAPRIYA	3	2	2	6	4	4	1	1	2	3
28	SUNDARAMURTHY	3	1	2	4	2	1	1	1	2	1
29	GURUSARANAN	3	1	2	6	3	2	1	1	2	1
30	AYSHA MINCY	3	2	1	5	3	3	1	1	1	1
31	SHEIK MOHAMMED	3	1	3	2	2	2	1	1	2	3
32	KALEESWARI	3	2	1	6	1	1	1	1	1	3
33	AKSHAYA	3	2	2	7	2	1	1	1	2	3
34	PERIYASAMY	3	1	1	7	2	1	1	1	1	1
35	RUBEN	3	1	3	7	4	4	1	1	3	1
36	SURUDHIKA	3	2	2	5	4	3	1	1	2	3
37	SUHANA	1	2	2	3	2	2	1	1	2	3
38	RAJESH	3	1	2	6	3	3	1	1	2	3
39	ABUBAKER	3	1	3	5	4	3	1	1	3	2
40	SANJAY	3	1	2	3	2	2	1	1	2	1

41	VISHAL	3	1	2	7	3	3	2	1	4	3
42	SIVASANKAR	2	1	2	2	4	4	1	1	2	3
43	YAMINI	3	2	2	6	3	2	1	1	2	1
44	LAKSHITHA	1	2	1	7	3	2	1	1	2	1
45	GURUHARISH	3	1	2	6	3	2	1	1	2	3
46	MUHAMMED RIYAS	3	1	2	5	1	1	1	1	2	3
47	AMINA	2	2	2	2	3	2	1	1	2	1
48	LOGAPRIYA	3	2	2	3	2	1	1	1	2	1
49	VASEEKARAN	3	1	2	6	3	2	1	1	2	1
50	SUDARSAN	2	1	1	4	2	1	1	1	2	3
51	ANUSHA	3	2	2	7	3	3	1	1	2	3
52	AVILA EVANGALIN	3	2	2	6	3	2	1	1	2	3
53	SANGEETHA	3	2	2	5	1	1	1	1	2	1
54	THANURDHARAN	1	1	2	6	3	3	2	1	4	3
55	LATHA	3	2	2	5	2	1	2	1	4	3
56	SRI GOPINATH	3	1	2	4	1	1	1	1	2	3
57	SHAMSIYA SHERIN	2	2	2	2	3	3	1	1	2	1
58	SHAHANA	3	2	2	3	3	2	1	1	2	1
59	SANJAY	3	1	2	3	4	4	1	1	2	3
60	AKSHAYA	2	2	2	3	3	2	1	1	2	1
61	AKSHAYA DHARSIN	3	2	2	7	1	1	1	1	2	1
62	REESHMAN MINA	3	2	1	2	3	2	1	1	1	1

63	ABDULLA	3	1	2	3	2	1	2	1	4	1
64	SADHANA	3	2	2	7	4	4	1	1	2	1
65	KAMNA	3	2	1	4	3	3	2	1	2	1
66	DHARANI	3	2	2	3	3	2	1	1	2	1
67	RAMYA	3	2	2	5	2	1	2	1	4	3
68	KAVYA	1	2	1	4	3	3	1	1	1	3
69	ROSHAN	3	1	1	2	1	1	1	1	1	3
70	SARANYA	3	2	2	5	2	1	1	1	2	3
71	AARON	3	1	2	3	2	1	1	1	2	1
72	DIVYA DARSINI	3	2	2	7	4	3	1	1	2	1
73	JASMINE PARVEEN	3	2	2	4	3	1	1	1	2	3
74	NISHANTH	3	1	1	7	3	2	1	1	1	3
75	BHARGATH NISHA	3	2	2	5	2	1	1	1	2	3
76	SAKTHIVEL	3	1	2	5	3	2	1	1	2	3
77	SRINITHI	2	2	2	6	2	1	1	1	2	3
78	SANDHYA	3	2	2	6	4	4	1	1	2	1
79	SOPNA	3	2	1	6	3	2	1	1	1	3
80	NITHYASREE	3	2	1	5	4	3	1	1	1	3
81	MONISHA	2	2	1	6	2	2	1	1	1	1
82	SAJATH HUSSAIN	1	1	1	4	2	2	2	1	4	3
83	JANANI	3	2	3	6	4	4	1	1	3	2
84	MONIKA	2	2	2	5	2	2	2	1	2	2

85	INIYAN	3	1	2	5	2	1	2	1	4	1
86	PAVIYARASAN	2	1	2	4	3	2	1	1	2	3
87	MITHRA	3	2	2	6	2	2	2	1	4	3
88	DHANUSRI	3	2	2	6	1	1	1	1	2	1
89	SAFRASERIN	2	2	1	3	1	1	1	1	1	3
90	ARSAYA FATHIMA	2	2	2	6	2	1	1	1	2	1
91	MANOJ KUMAR	3	1	1	5	3	2	2	1	4	3
92	NAFEELA	3	2	2	7	4	3	2	1	4	1
93	GOWSHIK	3	1	1	5	2	1	2	1	4	3
94	GOKUL	3	1	1	5	3	2	1	1	2	1
95	UDAYA CHANDRAN	3	1	2	4	2	1	1	1	2	3
96	SUBIKSHA	2	2	2	6	3	4	1	1	2	3
97	LITHIKA	3	2	2	6	3	2	1	1	2	3
98	JEEVANTHIKA	2	2	3	7	1	1	2	2	4	1
99	YAMUNA	3	2	2	5	3	2	1	1	2	1
100	YOGESH	3	1	2	7	4	3	1	1	2	2
101	LAVANYA	2	2	2	5	2	1	2	1	4	3
102	RESHMA	3	2	1	6	2	1	1	1	1	3
103	VISHALINI	3	2	2	5	2	1	1	1	2	3
104	VIDHUBALA	3	2	2	5	3	2	1	1	2	1
105	DHARANI	2	2	2	6	4	4	1	1	2	3
106	RAKSHITHA	2	2	2	4	3	3	2	1	4	3

107	RAKSHANA	3	2	2	3	2	1	1	1	2	1
108	RAKSHAYA	3	2	2	3	1	2	2	1	4	3
109	KAMATCHI	2	2	1	3	3	1	1	1	2	3
110	GOWTHAM	3	1	2	4	3	2	1	1	2	1
111	RIFAS	3	1	2	4	2	1	1	1	2	1
112	MANOHARAN	3	1	1	6	4	4	1	1	1	3
113	GAYATHRI	3	2	2	7	2	1	1	1	2	3
114	HARSHAVARTHAN	3	1	1	4	3	1	1	1	2	1
115	HARIKARAN	3	1	1	4	2	2	1	1	2	1
116	ABHINESH	3	1	2	5	3	3	1	1	2	3
117	AKASH	3	1	2	7	2	1	2	1	4	1
118	VIGNESH	3	1	2	4	3	2	1	1	2	3
119	DHANUSREE	3	2	2	5	1	1	1	1	2	3
120	TAMILARASAN	3	1	2	7	4	3	1	1	2	3
121	HARINI	3	2	2	4	3	2	1	1	2	3
122	KESAVAN	2	1	2	6	3	2	1	1	2	1
123	VARUN	3	1	1	5	2	1	2	1	4	1
124	MIDHUN	3	1	1	7	3	3	1	1	1	3
125	BALAJI	3	1	2	6	3	2	1	1	2	1
126	AYSHA	1	2	1	6	2	2	1	1	1	3
127	ASHWITHA	2	2	2	3	2	1	2	1	4	1
128	MOHAMMEDASHIK	3	1	2	5	3	3	1	1	2	1

129	NALAMATHI	3	2	2	4	2	1	1	1	2	1
130	BHAVANI	3	2	2	2	2	2	2	1	4	2
131	THEJESWARAN	2	1	2	4	2	1	2	1	4	3
132	HRITHIK	2	1	2	3	2	2	2	1	4	3
133	MOHAMMED	2	1	2	5	3	3	1	1	2	3
134	SOWMYA	2	2	1	5	3	2	1	1	1	1
135	ROSHNI	2	2	1	4	2	2	1	1	1	3
136	ASWIN	2	1	2	3	2	2	1	1	2	3
137	SURYA	3	1	2	6	4	3	1	1	2	1
138	PRASANNA MARY	3	2	2	5	1	1	1	1	2	3
139	SANJAY	2	1	2	2	1	1	2	1	4	3
140	DHRUVATHEY ALAN	2	1	2	3	2	2	1	1	2	1
141	GOURI	3	2	2	7	4	2	1	1	2	1
142	ANJALI	3	2	2	3	2	2	2	1	4	3
143	AZHAGARSWAMY	3	1	2	3	4	3	1	1	2	3
144	GOKUL	3	1	2	5	2	1	2	1	4	1
145	PADMAPRIYA	3	2	1	4	3	2	2	1	4	1
146	KABILASH	2	1	1	4	3	2	2	1	4	3
147	SUNILKUMAR	2	1	2	3	3	2	2	1	4	1
148	JANANI	3	2	1	3	3	2	1	1	2	3
149	BHOOMIKA	3	2	2	3	3	3	2	1	4	3
150	PRATAP	3	1	2	7	4	3	1	1	2	3

151	AJAY	1	1	2	3	3	2	1	1	2	3
152	KARTHIKEYANI	3	2	2	6	3	2	1	1	2	1
153	ADHINI	2	2	1	6	3	2	1	1	1	1
154	PREETHI	3	2	1	6	3	3	2	1	4	3
155	JAYASURYA	3	1	1	2	2	1	2	1	4	1
156	SHARMITHA	3	2	2	3	2	1	2	1	4	3
157	SIVAKARTHIKA	2	2	2	2	3	2	1	1	2	1
158	PRIYADARSINI	3	2	1	5	2	2	2	1	4	1
159	GIRI	2	1	2	2	1	1	1	1	2	1
160	VISHNU	2	1	1	3	2	1	2	1	4	3
161	JITHIN	3	1	2	5	1	1	2	1	4	3
162	MRITHULA	3	2	1	2	1	1	1	1	1	3
163	KISHORE	2	1	2	2	3	4	2	1	4	1
164	ASHMA	2	2	1	3	3	3	2	1	4	1
165	DHARAN	3	1	2	5	2	2	2	1	4	3
166	MOHAMMED IRFAN	3	1	1	3	2	1	2	1	4	3
167	PRIESELLA	3	2	2	3	2	1	1	1	2	3
168	KAVIYARASU	1	1	2	3	2	1	1	1	2	2
169	FATHIMA NAZRIN	3	2	1	7	2	1	1	1	1	1
170	HARSHAVARDAN	3	1	1	7	2	2	1	1	1	3
171	PRANADESHWARI	2	2	2	4	1	1	2	1	4	3
172	DIVYASRIDHAR	3	2	1	6	4	4	1	1	2	1

173	SRIDHAR	3	1	1	3	2	1	1	1	2	1
174	SANTHOSH	2	1	2	7	2	3	2	1	4	3
175	YOGESWARAN	2	1	1	7	1	1	2	1	4	3
176	GOWRI PRASANTH	2	2	1	4	2	1	2	1	4	1
177	ANBU	3	1	2	2	3	3	2	1	4	1
178	GOWRI	3	2	1	4	2	1	2	1	4	2
179	DEVA	3	1	2	3	3	2	2	1	4	3
180	SHARMILA	3	2	1	6	4	3	1	1	2	3
181	SHYAM PRADEEP	3	1	1	3	2	1	1	1	1	3
182	HEMALATHA	2	2	2	6	3	3	1	1	2	1
183	LOGANATHAN	2	1	2	6	3	2	1	1	2	3
184	MANIKANDAN	2	1	2	3	1	1	1	1	2	3
185	USSAIN	3	1	2	3	2	1	2	1	4	1
186	SAFANA	2	2	2	7	2	2	1	1	2	3
187	KOUSIYA	2	2	2	7	2	1	1	1	2	3
188	TUKIN	3	1	2	7	4	3	1	1	2	1
189	KAVIBHARATH	3	1	2	4	2	1	1	1	2	1
190	ANSIFA	3	2	1	3	3	2	1	1	1	3
191	DHARANYARAJ	2	1	2	2	3	2	1	1	2	3
192	YAKSHINI	3	1	2	6	3	2	2	1	4	1
193	PERIYASAMY	3	1	2	6	3	3	2	1	4	1
194	BHUVANESWARI	3	2	2	3	3	2	1	1	2	3

195	RAJANISH	3	1	1	3	1	1	1	1	1	1
196	HARSHADA	3	2	1	3	2	1	1	1	1	3
197	VISHNUVARDHAN	3	1	2	2	3	2	2	1	4	3
198	SAIBHUVANESHWARI	3	2	2	6	3	3	2	1	4	3